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EDITORIAL

The new editorial staff takes this opportunity of wishing you all a happy and prosperous new year! To the newly graduated "men in white" we offer our congratulations and wish you every success in the years to follow.

The Journal

The University of Toronto Medical Journal is a democratic institution, the function of which is essentially the expression of student thought. It is published for the students and by the students. It is the students' Journal, and their common responsibility. If there is to be a Journal it must have the full support of the student body in the form of contributions for its pages. It is the constant desire of the editors that more and more students use this Journal as a mode of expression and a source of information. This Journal has been in existence for 20 years and has fulfilled its purpose well during this period. May it continue to do even more for the furtherance of education of medical students in years to come. This is not a plea for articles; this is a reminder of the opportunity which is almost unique in the medical schools of this continent—the freedom of thought, word and deed which today allows us to come forward and express ourselves unhampered by the fears of dictatorship.

A few years ago the office of pre-clinical editor was established with the hope of receiving more material for and from the junior years. We would remind the pre-clinical students that this is also their Journal and that our desire to publish

more articles of interest to them can be fulfilled only with their cooperation. Many outstanding articles have arisen from the pens and cerebrations of students of the first three years, and we feel confident that many more such articles will be forthcoming.

Since the calendar "year" and the academic "year" no longer coincide as they did in pre-war days, only 2 issues of Vol. XX have been published. The new editorial staff hopes to produce the other 4 issues which will complete this volume and for which our subscribers have already paid. This task cannot be accomplished without articles for publication. This material we hope will come primarily from students—not, of course, wishing to discourage those members of the staff whose timely contributions in the future will be just as welcome as they have been in the past.

Congratulations are due Gordon Stewart and his outgoing editorial staff who did so well to publish even two issues last Fall, under the stress and strain of a wartime curriculum which no doubt acted as a deterrent to those students who might otherwise have contributed to our pages. We have emphasized that this is the students' JOURNAL, but we sincerely hope that our graduates will augment the ever-growing list of subscribers.

UROLOGY AWARD

The American Urological Association has asked us to publish the following announcement in our JOURNAL:

"*Urology Award*—The American Urological Association offers an annual award 'not to exceed $500' for an essay (or essays) on the result of some specific clinical or laboratory research in Urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years.

"The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, May 31—June 3, 1943, Hotel Jefferson, St. Louis, Missouri.

"Essays must be in the hands of the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 1, 1943."

BACK ISSUES

We would remind our subscribers that back issues are available at the rate of 10c. per copy. Those wishing any of these issues address Mr. F. C. Jones, University of Toronto Medical Journal, 107 Anatomy Building.

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BRIGHT'S DISEASE

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The purpose of this paper is to present a review of the subject of Bright's Disease for students. It is not pretended that this presentation will be exhaustive in detail, but rather that it will serve as a guide in their studies of an admittedly difficult subject.

The term "Bright's Disease" is intended to cover a group of degenerative, inflammatory, and vascular diseases of the kidneys for which no definite causes have been found. The classification used in this article is that used commonly in clinical teaching.

I. Degenerative Bright's Disease — Chronic Lipoid Nephrosis.

II. Inflammatory Bright's Disease.
   1. Acute Diffuse Glomerulo-Nephritis.
   2. Subacute Diffuse Glomerulo-Nephritis.
   3. Subchronic Diffuse Glomerulo-Nephritis.
   4. Chronic Diffuse Glomerulo-Nephritis.

III. Vascular Bright's Disease
   1. Essential Hypertension.
   2. Malignant Hypertension.

IV. Chronic Pyelonephritis.

It is necessary, at the outset, to remember that the kidneys are a pair of highly vascular organs whose function it is to rid the blood stream of the waste products of metabolism brought to them by way of the renal arteries. This function is performed by the action of thousands of microscopic units called nephrons. Each nephron is composed of a filtering head called a glomerulus and a system of tubules which conveys the glomerular filtrate to the renal pelves. In the course of its journey, the glomerular filtrate becomes concentrated by the reabsorption of water, salt, and other crystalloids. It is considered that, under resting conditions, a limited number of nephrons are functioning; as the work of the kidneys increases, the number of functioning nephrons likewise increases, until the majority or all are engaged in clearing the blood of waste products. Nature has endowed man with a great renal reserve—so much so that it is possible to lose three-fourths of the total renal functioning tissue without the supervention of renal failure.

It will be clear to anyone who studies the subject of Bright's Disease that there are five clinical phenomena that require some understanding before we proceed to a discussion of the various forms.

1. Albuminuria

It is generally considered that albumin found in the urine is the same as that found in the blood, and that the phenomenon reflects a state of increased permeability of the capillary tufts of the glomeruli. Recent investigations by Addis, however, have cast some doubt on the above hypothesis. It has been shown that the glomerular filtrate may contain albumin normally, and that such albumin is normally reabsorbed by the tubules. The explanation of the finding of albumin in the urine might then be defective tubular reabsorption, increased glomerular permeability, or a combination of both. In heart failure it is possible that increased hydrostatic pressure in the glomeruli may be an alternative or added factor.

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2. Oedema

This condition may be defined as the occurrence of an increased quantity of fluid within the peripheral intercellular spaces. A puffy appearance is imparted to the part, and the pressure of an examining finger leaves a pit or depression that is slow in disappearing. There are eight well-known types of oedema, but only three will be mentioned here because they alone have a bearing on the subject of Bright's Disease.

(a) Nephritic Oedema

This type is characteristically found in the non-dependent parts of the body, especially in the loose peri-ocular areolar tissues. It is considered to be a manifestation of increased capillary permeability of a widespread character. The oedema fluid contains no globulin but about 1% of albumin.

(b) Nephrotic Oedema

This variety of oedema is also widespread in distribution and is not confined to the dependent parts of the body. It is due to a pre-renal deviation of the water and salt produced by a marked reduction in the osmotic pressure of the blood as a result of depletion of the blood albumin by prolonged albuminuria. It is not believed that the capillaries are abnormally permeable anywhere in the body but in the glomerular tufts. The principles of the Donnan equilibrium govern the transudation of water and salt from the blood to the tissue spaces. The concentration of albumin in this oedema fluid is, therefore, low—less than 0.1%.

(c) Cardiac Oedema

This type of oedema is characteristically dependent in distribution and, as Starling has shown, is due to the increased hydrostatic pressure of the blood in the terminal capillaries as a result of myocardial weakness. There may be also some degree of increased capillary permeability as a result of disturbed nutrition of the parts. The albumin content is about 0.7%, i.e. intermediate between that of nephritic and nephrotic oedema.

3. Azotaemia, or Renal Insufficiency

The excretion of nitrogenous products, such as urea and creatinine, is, perhaps, the most important function of the kidneys. This constant regulating mechanism is reflected in health by an N.P.N. content of the blood that lies between 25 and 35 mg. per 100 c.c. It is believed that these nitrogenous materials pass through the glomerular tuft by a process of filtration. In the absence of glomerular filtration, nitrogen excretion fails to occur and the N.P.N. content of the blood begins to rise above its normal figure. As mentioned above, such does not occur until more than three-quarters of the functioning nephrons are destroyed. The occurrence then, of nitrogen retention may be evidence of severe renal damage, either transient or permanent. The retention of nitrogenous products, urea and creatinine, will not of themselves produce true uraemia; nitrogen retention, however, is always present in high degree when true uraemia exists, i.e. nitrogen retention is always a part of the clinical picture of true uraemia. Renal disease is only one of several causes of nitrogen retention but it is probably the commonest. True uraemia is a fatal toxaemia due to failure of renal function, with N.P.N. levels that may reach 300 mg. per 100 c.c. Usually, some degree of hypertension co-exists, but not necessarily so; the blood pressure may be quite normal. These patients exhibit a slowly progressive apathy leading to a state of mental stupor and coma. Mus-

cular twitchings occur but epileptiform convulsions are seldom seen. The twitchings are probably due to tetany produced by the low serum calcium in this condition. An increasing acidosis is evidenced by a declining CO_2 combining power of the blood and the development of Kussmaul breathing. Death occurs in a state of deep coma.

4. Hypertension

Hypertension is said to exist whenever the blood pressure exceeds 140/92/90, the last figure being the diastolic fifth point taken at the total disappearance of all sound. In general, it is believed that a high diastolic pressure is more important than a high systolic. Since hypertension is present in all forms of Bright's Disease except nephrosis and early subchronic nephritis, it is very important to have some understanding of its production.

There is a type of individual known as a vascular hyperreactor who reacts abnormally to nervous stimuli. A sudden shock, such as immersing the hand for a few seconds in ice water causes an abnormal rise in the blood pressure and in the pulse rate. These individuals are jumpy and high-strung, and probably form the pool from which cases of Essential Hypertension are recruited. It would thus appear that a neurogenic basis underlies early high blood pressure.

On the other hand, the results of many investigations of the last decade have proved beyond all doubt that a humoral mechanism, by means of a vaso-pressor substance, is a cause of experimental hypertension in animals. The similarity of the lesions so produced to those found post-mortem in man suggests strongly that some such humoral mechanism exists in many forms of human hypertension. It appears that partial renal ischaemia causes the elaboration of a substance called renin within that kidney. In animals, this partial ischaemia may be produced by a silver clamp placed on the renal artery. Although not proven, it appears that in man a state of functional hypertonus of the afferent arterioles to the glomeruli may cause a similar production of renin by a state of partial ischaemia, and resultant decreased renal blood flow. The substance renin, being washed out of the kidney by the venous blood, unites with a substance normally present in the bloodstream called renin-activator or preangiotonin. The result is the production of a true pressor substance called angiotonin, or hypertension. Exactly how angiotonin produces hypertension is not known; presumably, it does so by exerting a spastic effect on the splanchnic arterioles, thereby raising the peripheral resistance. The effect of the increased peripheral resistance is to raise the diastolic blood pressure which, in turn, increases the work of the left ventricle of the heart, which is reflected by a rise in the systolic blood pressure. It appears from recent work of Wilson and Byrom that a vicious circle is thereby established and that the raised pressure causes further obliterative changes to occur in the vulnerable arterioles of the kidney. The result of this process is probably the further production of renin and a resulting increase in hypertension and damage to the cardio-vascular system. It will be clear, then, that any chronic disease that diminishes progressively the blood supply to the kidney can set up a vicious circle that leads eventually to sustained hypertension. Thus it is that essential hypertension, chronic diffuse nephritis, chronic pyelonephritis, hypertensive renal disease following toxaemia of pregnancy, and the chronic hypertension of lead workers, may all produce a

hypertensive disease state that in the end stages may be so similar that only the history would serve to differentiate them. It is important, therefore, to realize that, while we must have some form of working classification of Bright's Disease, the divisions and subdivisions are by no means always clearcut. Indeed, more often than not, the patient presents a very mixed picture.

5. Hypertensive Encephelopathy

Irrespective of the cause of the hypertension, there emerges, in certain cases of Bright's Disease, a clinical syndrome characterized by convulsive epileptiform seizures which are due entirely to the hypertensive state. This clinical syndrome used to be confused with true uraemia, but is now easily recognized by the characteristic convulsions, the elevated blood pressure, and the normal, or but moderately elevated, non-protein nitrogen in the blood.

It is believed that hypertension is associated in these cases with an abnormal tendency to cerebral arteriolar spasm. This condition produces a state of cerebral ischaemia, with or without cerebral oedema. The result is a convulsive seizure with a very high blood and cerebrospinal fluid pressure. It can be treated very successfully by venesection, lumbar puncture, and by dehydrating measures such as the intravenous administration of 50% glucose or sucrose. These measures, however, afford but temporary relief and the patient usually dies of a massive cerebral haemorrhage or cardiac failure.

With these clinical phenomena in mind, we may now proceed to a discussion of the various forms of Bright's Disease. Although widespread pathological changes occur, with few exceptions, only those changes found in the kidneys will be described.

I. Degenerative Bright's Disease—*Chronic Lipoid Nephrosis*

Chronic Lipoid Nephrosis or Pure Nephrosis is the only disease that will be considered under this title. It is true that poisoning by heavy metals and amyloid disease will cause degenerative changes in the kidney, but these conditions are not usually considered examples of Bright's Disease.

Definition: Nephrosis has been well defined by T. Izod Bennett as a name applied to a group of rare cases exhibiting albuminuria and a tendency to oedema, but without any history of haematuria or other evidence of acute nephritis, and without any signs such as hypertension, cardiac hypertrophy, and retinitis to indicate involvement of the cardiovascular system.

Etiology: The cause of the disease is unknown. Some observers deny the existence of the disease; some believe it to be a form of mild nephritis. It occurs almost exclusively in children and young adults.

Pathological Changes. Macroscopic: The kidney is of the "large white" variety, being considerably enlarged, soft, and oedematous. The capsule is readily stripped from the smooth, pale, glistening surface which is thickly encrusted with opaque creamy-yellow flecks. On section, the cortex is wide and sharply demarcated from the darker medulla. The pattern is straight but slightly blurred. In some cases, it is of a uniform creamy-yellow colour; in others, it presents a variegated appearance with alternating sections of opaque creamy masses and pale translucent renal tissue. Long radiating yellowish streaks descend into the pyramids of the medulla.

Microscopic: There is an absence of proliferative changes in the glomeruli, and a complete absence or very slight amount

of any inflammatory infiltration. The conspicuous feature is a widespread lipoid infiltration of the tubular epithelium. Anisotropic fat droplets are deposited extensively in the proximal convoluted tubules and the ascending limbs of the loops of Henle. The nuclei of these cells are degenerated and there are many hyaline and granular casts in the lumina. The interstitial tissue, particularly the periglomerular and adventitial, is oedematous. Interstitial infiltration is usually absent, but if present is extremely slight in amount and of low grade, consisting almost exclusively of lymphocytes and plasma cells.

Chemical Pathology: The most important chemical change in nephrosis is a very great diminution in the plasma proteins. This diminution is at the expense more of the albumin than of the globulin fraction. The albumin content of the plasma falls from 5 to less than 2 grams per 100 c.c. while the globulin remains at about 2 to 2.5 grams. It is the fall in the osmotic pressure of the blood consequent on the loss of albumin that is the cause of the pre-renal deviation of water and salt and the resulting nephrotic oedema.

The cholesterol content of the blood is increased in nephrosis well above the normal level of 170 mg. per 100 c.c.; often the level approaches 500 mg. per 100 c.c., and levels as high as 1000 mg. per 100 c.c. have been recorded. There appears to be little doubt that the cholesterol ester found in the kidney is deposited there from the over-charged blood and that the tubular change is not a degeneration but a true infiltration. This cholesterol ester is cholesterol oleate or palmitate. In association with the hypercholesterolaemia and renal deposition of ester, various amounts appear in the urine and can be detected by the heat test under polarised light. Normally, 1.7 to 4.2 mg. are excreted daily; in nephrosis, as much as 16 to 42 mg. are excreted daily. It seems probable that the glomeruli are abnormally permeable, not only to albumin but also to cholesterol ester.

No complete explanation has been found for the hypercholesterolaemia of nephrosis. It seems likely that it is associated in some way with the deficit of serum albumin, possibly a reflection of a state of malnutrition. The fat content of the diet bears no relation to the level of the blood cholesterol, although raising the intake of ingested fat does tend to increase the level of neutral blood fat—a lipaemia that also may occur in nephrosis. Despite the great elevation of the blood cholesterol, oedema fluid and transudates, though frequently opalescent, have a low cholesterol content (1.5 to 0.5 mg. per 100 c.c.). This finding, together with the presence of a low protein content, suggests that abnormal capillary permeability plays no part in the production of nephrotic oedema.

The blood calcium in nephrosis is somewhat reduced, while tests of renal function give figures very little, if at all, below those of normal health. Nitrogen retention does not occur and there is no inability to excrete salt or water. The oliguria that occurs is due to the pre-renal deviation of salt and water to the tissues.

Clinical Picture: Nephrosis occurs usually in a child or young adult. Often it is discovered in its early stages by a routine medical examination when heavy, constant albuminuria is found unaccompanied by the presence of red blood cells or granular casts. The individual otherwise feels and looks completely well with no oedema or hypertension and with perfectly normal renal-function tests. The

examination of the heart and ocular fundi reveals no abnormality. Sooner or later, however, weakness and the appearance of oedema attract attention. The oedema is observed first in the dependent parts, but later is seen in the thighs, scrotum, abdominal wall, thoracic wall, back and face. Ascites, and later hydrothorax, often develop. The basal metabolism is low—about —20%. Anaemia is usually absent, although occasionally present in marked degree and of secondary type with low colour index.

The subsequent course of nephrosis is that of persistent stubborn massive oedema associated with heavy albuminuria and oliguria. The disease continues for months or years with fluctuating periods of remission and relapse. Often the patient's hopes are raised by diuresis and the temporary decrease or disappearance of oedema. Only too often they are dashed to the ground by the sudden reappearance of massive dropsy. The disease is particularly trying, for the patient feels otherwise in good health. Occasionally, the oedema disappears while the albuminuria persists, and, rarely, both oedema and albuminuria disappear when the patient makes a spontaneous recovery. It would appear that, when recovery occurs, the leak of albumin through the glomerular tufts ceases, allowing a replenishment of the serum protein and a restoration of the colloid osmotic pressure of the blood. Possibly there is an improved re-absorption of albumin by the tubules. More often, however, secondary infections, such as pneumococcal peritonitis, bronchopneumonia, or streptococcal septicaemia, cause a fatal termination.

Differential Diagnosis: Chronic Lipoid Nephrosis must be differentiated from subchronic nephritis. The distinction is made only by prolonged study and observation. A history of an antecedent attack of acute glomerulo-nephritis makes one favour subchronic nephritis, but this diagnosis is established by the appearance of haematuria, hypertension, changes in the fundi, and a rising blood non-protein nitrogen. Such changes never occur in pure nephrosis.

Treatment: The most important items in the treatment of nephrosis are prolonged rest in bed, a diet with about 70 to 80 grams of protein per day, and the maintenance of morale by the provision of a bright environment and an attitude of cheerful confidence in the outcome.

In accord with Epstein's teaching, a diet with a liberal quantity of protein is provided in order to replace the albumin lost in the urine. It has been found that a diet containing 100 grams or more of protein per day is impracticable, for the average nephrotic patient will not eat it. It is essential to restrict all salt in the diet and to reduce the daily fluid intake to 1200 to 1500 c.c. Thyroid extract may be given and is occasionally dramatically successful. Peculiarly enough, however, even large doses more often have little effect. If anaemia be present, it is wise to administer iron in the form of Ferrous Sulphate gr. V t.i.d. with meals. Since haematuria and nitrogen retention are absent, it is permissible to try the effect of intravenous salyrgan, preferably after the administration of 90 grains of ammonium chloride. If no significant diuresis results, it should not be repeated. It is very essential to remove all foci of infection in the body—notably diseased tonsils and teeth. Large collections of fluid in the serous cavities, hydrothorax, and ascites, are removed by mechanical drainage when they fail to disappear by diuretic measures. Decapsulation of the kidneys has found no convincing support.

Pneumococcal secondary infections should be treated by an appropriate course of sulphathiazole or sulphadiazine, paying particular attention to possible urinary complications.

II. Inflammatory Bright's Disease

1. *Acute Diffuse Glomerulo-Nephritis (Synonyms: Acute Diffuse Nephritis, Acute Toxic Nephritis, First Stage Glomerulo-Nephritis)*

Definition: Acute Diffuse Glomerulo-Nephritis is an acute inflammation of the glomeruli of the kidneys, which is associated with evidence of widespread capillary damage throughout the body.

Etiology: The exact mechanism by which acute nephritis arises is unknown. The disease almost always follows an acute upper respiratory infection, or some other acute infection such as scarlet fever or erysipelas. Infections due to the haemolytic streptococcus have been regarded with more suspicion than those caused by other micro-organisms. A great deal of investigation has been carried out in an effort to elucidate the etiology of acute nephritis because it is believed generally that other forms of Bright's Disease are causally related to an antecedent attack of acute nephritis. It is significant that the attack characteristically occurs, not during an acute infection, but about ten to fourteen days after that infection has subsided. Furthermore, it is usual for an acute nephritic to excrete a sterile urine; cultures from the kidneys of a patient, post-mortem, are sterile. The blood of an acute nephritic fails to yield living organisms. For these and other reasons, it is believed that acute nephritis is not an acute infection in the kidneys but an unusual form of allergic response characterized by spasm and later leakage of capillaries throughout the body. The capillaries of the glomerular tufts of the kidneys appear to be the most vulnerable and the most damaged of the body. Certainly, the whole course of the disease is dominated by the progress of the renal lesions. In the majority of cases, the process is reversible and complete recovery occurs; it is believed, however, that chronic nephritis is always antedated by an attack of acute nephritis, possibly so mild that it is not remembered by the patient. Campbell has called attention to the wisdom of making a routine of examining the urine within a few days of recovery from all acute respiratory infections. It is probable that this measure will reveal instances of mild acute nephritis which would otherwise be overlooked, and which might, if neglected, later contribute to the number of "idiopathic" chronic nephritides. Exposure to cold and wet is an important predisposing factor in the development of the disease.

Pathological Changes. Macroscopic: Both kidneys are involved and are usually slightly enlarged, grayish or reddish in colour, soft in consistency, and studded with tiny red haemorrhagic dots. The capsule strips readily and, on section, the cortex is well demarcated from the medulla which is of a congested purplish-brown colour. Haemorrhagic glomeruli are noted as red dots throughout the cortex.

Microscopic: Attention is focussed on the glomeruli which are almost all involved from the earliest stages. The typical glomerulus is enlarged, highly cellular, and often almost bloodless due to swelling and proliferation of the capillary endothelium. The partial or complete occlusion of the capillary lumina by this process severely impedes, and occasionally obstructs completely, the circulation of blood in the glomeruli. This highly-

cellular swollen glomerulus is described by Russell as "proliferative glomerulitis". In addition to these proliferative changes in the cells of the tufts, the glomeruli are invaded by numbers of neutrophilic leucocytes which occupy the capillary lumina and often the stroma of the tuft. Hyaline thrombi are sometimes present in the capillaries of the tufts, and occasionally red blood cells and neutrophilic leucocytes are observed in the capsular spaces.

The tubular epithelium of the kidneys shows widespread albuminous and dropsical degeneration. In addition, when the inflammatory changes in the glomeruli are intense, hyaline droplet degeneration of the tubular epithelium is obvious, whereas, when the changes are mild, fatty and especially lipoid degeneration occurs.

The lumina of the tubules contain large numbers of red blood cells and a variable number of neutrophilic leucocytes. Granular and hyaline casts are commonly seen in the loops of Henle and in the collecting tubules.

The interstitial tissue is frequently oedematous, but there is no fibrosis or any evidence of proliferation of fibroblasts. There is remarkably constant infiltration of the peri-glomerular tissues with neutrophilic leucocytes; the same infiltration is observed in the periadventitial tissues of the vasa afferentia.

The other blood vessels of the kidneys show no gross abnormalities. Haemorrhage occurs occasionally into the tubules and less frequently into the interstitial tissues.

The pathological changes in the body, other than the kidneys, have received scant attention. Ellis has stressed the fact that the heart is embarrassed in certain cases of acute nephritis, particularly in children. A certain degree of cardiac enlargement occurs, but there are no detailed accounts of changes in the coronary arteries in fatal cases.

The oedema of acute nephritis is usually widespread, and is due to damage and increased permeability in the parts affected.

Chemical Pathology: There is a slight to moderate degree of impairment of renal function in cases of acute nephritis that do well. It is common to observe transient nitrogen retention with N.P.N. levels of 50 to 60 mg. per 100 c.c. of blood. Severe fatal cases of acute nephritis die a uraemic death with very severe impairment of renal function and N.P.N. levels of 100 mg. or more per 100 c.c. of blood.

Clinical Picture: Typically, acute nephritis occurs in children and young adults. The onset is usually fairly sudden—about ten to fourteen days after an acute upper-respiratory infection. Attention is attracted to the patient by the development of oedema around the eyes and the frequent passage of scant, dark, smoky or bloody urine. The oedema spreads to involve the whole face and usually the trunk and lower extremeties. Often the patient complains of headache, pain in the back over the kidneys, anorexia, nausea, and sometimes vomiting. The temperature is usually elevated slightly to 99 or 100°F.; occasionally, high fever and chills occur. The pale, pasty, puffy appearance of the patient suggests an anaemic condition. The examination of the blood, however, reveals a normal haemoglobin and red-blood count. The white-blood count is normal or somewhat elevated. Examination of the heart in children occasionally reveals slight but definite enlargement. This enlargement is accompanied by moderate hypertension and a variable degree of dyspnoea. More often, the heart is normal in size and there are no subjective symptoms of cardiac insufficiency.

A moderate transient elevation of the blood pressure is, however, a fairly constant finding.

The urine characteristically is passed frequently and is small in amount. It contains gross and microscopic blood in large quantities, much albumin, numerous pus cells, and large numbers of granular and red cell casts. The specific gravity of the urine is high—1022 to 1032.

The average case of acute nephritis progresses favourably and ends in complete cure. In the course of three or four days, the oedema subsides, the urine becomes more abundant and lighter in colour, and such symptoms as headache, restlessness, sleeplessness, nausea, and vomiting disappear. The urine begins to clear as shown by decreasing albuminuria, haematuria, pyuria, and cylindruria. The casts disappear first and the blood and albumin last. Soon the patient is symptom-free, and before long has a normal urine and is considered cured. The average duration of an attack of acute nephritis is about six weeks.

Not all cases, however, follow the above course. The disease may be prolonged over several months before a cure results. During this time there is a fluctuating degree of oedema, haematuria, and albuminuria. Eventually, however, the symptoms and signs of the disease disappear.

A few cases follow a fulminating downhill course with massive albuminuria, haematuria, moderate oedema, and the development of sustained hypertension and renal insufficiency. The ability to concentrate the urine fails and the patient dies in a state of true uraemia, of hypertensive encephalopathy, or of cardiac failure.

Prognosis: Nearly all cases that can be recognized clinically recover. A few follow the atypical courses outlined above. Probably many cases are never recognized by either patient or doctor and are the cause of many insidious forms of inflammatory Bright's Disease seen in later life.

Differential Diagnosis: Acute focal nephritis may occur during the course of many acute infections. It is recognized and differentiated from acute diffuse nephritis by haematuria without casts, by the absence of oedema, hypertension and nitrogen retention, and by the fact that the disease occurs during an infection rather than ten to fourteen days after it. Subacute bacterial endocarditis causes its own form of focal nephritis and haematuria. It is recognized by finding the other usual signs of that disease.

Treatment: The essential of treatment is rest for the kidneys. This rest is accomplished by putting the patient to bed and by giving a diet that imposes the least work on the kidney compatible with the proper nutrition of the patient. It is usual to give him a diet of 800 c.c. of milk daily or 1000 c.c. of fruit juice (orange juice, grapefruit juice, etc.). The patient is kept strictly in bed and given full nursing care. He is kept on the above diet until the oedema is gone and the urine free of blood and albumin. Usually a period of one to two weeks is necessary to accomplish this result. At the end of this time the patient is allowed one portion of carbohydrate with each meal in addition to the usual milk. At the end of a week, if there is no return of albumin, he is allowed two portions of carbohydrate with each meal. At the end of another week, if still no albuminuria exists, he may be given a diet of CHO=250, P=40, F=80, salt-free, and fluids up to 1200 or 1500 c.c. daily. If a trace of albumin appears and lasts three days, the diet must be reduced to the previous lower level. If, at the end of a week on a high carbohydrate diet,

there is no urinary abnormality, the patient may start to sit up, and at the end of another week he may be allowed to walk. If the urine remains clear for two weeks, the protein may be raised to 60 grams, and subsequently to 80 grams per day. Thereafter, the patient should never eat more than 80 grams of protein daily. A return of albuminuria and haematuria indicates a return to bed rest and restricted diet. Only after the patient has been up and around and free of all signs of disease for three weeks should one consider removal of foci of infection.

Occasionally one encounters acute nephritis with persistent slight haematuria and albuminuria, despite the strictest dietetic and nursing care. These cases should be kept in bed for one month after all signs of improvement have ceased when they may be allowed up, for it is practically impossible to keep them in bed any longer.

It is important to emphasize the need for patience and prolonged rest to secure complete disappearance of all urinary abnormalities. A complete cure is possible only in the acute stage of nephritis. Once the disease becomes chronic, cure is no longer possible.

Diuretics have no place in the treatment of acute nephritis, nor is there any medicine that has a beneficial effect on the course of the disease. Sweating and other forms of physiotherapy are no longer employed. Surgical decapsulation of the kidney has not received the approval of the profession. It is important to warn the patient against subsequent exposure to cold and wet.

2. *Subacute Diffuse Glomerulo-Nephritis (Subacute Diffuse Nephritis)*

Definition: A disease which is really a progressive serious form of acute nephritis, characterized by remissions and exacebrations, and usually terminating in the uraemic death of the patient.

Etiology: The cause of this disease is the same as that of acute nephritis.

Pathological Changes. Macroscopic: The kidneys are enlarged and oedematous, and the colour varies from a grayish-red or pink to a deep mahogany red, according to the degree of congestion. Petechial haemorrhages are scattered over the subcapsular and cut surfaces, and specks of lipoid are frequently present. On section, the cortex is deep, the pattern blurred, and the demarcation from the medulla indistinct. The glomeruli appear to the naked eye as glistening gray dots. The medulla is marked by poorly-defined opaque white streaks.

Microscopic: The characteristic change noted in these kidneys as in the glomeruli where Bowman's capsule undergoes such marked proliferation that the so-called epithelial crescents or demilunes are formed. This change is described as "proliferative capsulitis" by Russell and is the hallmark of very severe inflammatory damage to the glomeruli. This finding is constantly present, but is unevenly distributed throughout the cortex; some glomeruli are markedly affected while others are but little changed or may escape entirely. Proliferative glomerulitis is also constant and affects all the tufts. It is common to observe adhesions between the tufts and the epithelial crescents growing up from the hyperplastic Bowman's capsules. These adhesive bridges are soon invaded by spindle fibroblasts with a resulting complete destruction by fibrosis of a large number of glomerular tufts. Leucocytic infiltration of the tufts and demilunes is always present and is also often noted in the capsular spaces. Hyaline droplet degeneration of the epithelial

cells of Bowman's capsule is frequently present.

The characteristic changes that occur in the tubules are albuminous, dropsical, hyaline-droplet, and lipoid degeneration of the epithelium. Hyaline-droplet degeneration predominates over lipoid degeneration, although both co-exist. The tubular lumina contain numerous red and white blood cells, desquamated epithelial cells, and all forms of casts, i.e. granular, leucocytic, red-blood cells, lipoid and hyaline.

Oedema and diffuse fibrosis are the changes that occur in the renal interstitial tissue. The fibrosis involves the cortex and outer medulla and is most marked around the glomeruli. The interstitial tissue is infiltrated diffusely with very numerous neutrophiles, eosinophiles, plasma cells, and small lymphocytes. Small haemorrhages sometimes occur and lipoid is occasionally seen in the interstitial spindle cells.

The interlobular arteries and vasa afferentia sometimes show acute necrosis with purulent infiltration of the vessel walls. Slight medial hypertrophy is sometimes observed.

It would appear that these cases with marked proliferative capsulitis of the glomeruli correspond to the "extra-capillary" glomerulo-nephritis of Fahr. Cases of Bright's Disease with marked proliferative glomerulitis and little or no proliferative capsulitis correspond to Fahr's "intra-capillary" glomerulo-nephritis. In general, the former represents a severe inflammation resulting in a stormy course and rapid death from uraemia; the latter indicates a milder course with recovery or a protracted low-grade chronic illness.

Chemical Pathology: These patients develop renal insufficiency at various times, in variable degree, and finally severely as a terminal result.

Clinical Picture: Subacute nephritis is the name given to those cases in which the urinary abnormalities, hypertension, oedema, impairment of renal function and other manifestations of the acute stage do not abate, and, in fact, are intensified so that death from uraemia results in a few months or, at most, two to three years. Most of the cases occur in the late thirties. These hapless victims follow a course of prolonged bed care with alternating periods of remission and relapse. Often when the physical and urinary signs are almost normal, a sudden flood of blood cells occurs in the urine with accompanying hypertension, morning headache and dyspnoea. This deterioration in the patient's condition is often precipitated by the occurrence of an upper-respiratory infection, especially a sore throat. Sooner or later, impairment of renal function becomes established with gradually mounting nitrogen retention. Death from uraemia is the usual outcome, although some physicians claim to have observed a cure in a very few cases.

Differential Diagnosis: These cases are to be differentiated from those with acute nephritis. The distinction is made by the usual favourable course of the acute nephritic within a reasonably short time of six weeks to two months. The difficulty lies in those cases of acute nephritis which take several months to heal. It may be impossible, in such cases, to tell just when acute nephritis ends and subacute begins. A story of repeated sore throats and resultant acute exacerbations of haematuria favours strongly a diagnosis of subacute nephritis.

Treatment: These patients are treated along the same lines as the acute nephritic. One must keep in mind constantly the nitrogen, water, and salt content of the diet. It may be necessary to steer a middle

course between the dangers of uraemia on one hand and the presence of oedema on the other. In this case, one regards nitrogen retention as a much more serious complication than oedema. It is necessary then to allow the patient sufficient fluid to excrete his nitrogenous waste in a dilute urine. Despite the presence of haematuria, one is forced in these cases to advise removal of foci of infection in order to protect the patient from repeated exacerbations. This step is taken despite the danger of throwing the patient into uraemia, for it is the only means of cure that is available. Sooner or later, however, nearly all the cases develop uraemia and receive the usual treatment for that condition. An account of the treatment of uraemia will be given under "chronic nephristic".

3. *Subchronic Glomerulo-Nephritis*
(*Chronic Parenchymatous Nephritis, Chronic Hydraemic Nephritis, Chronic Hydropigenous Nephritis, Chronic Nephritis with Oedema, Subacute Nephritis of some authors, Second-Stage Glomerulo-Nephritis*)

Definition: A form of Inflammatory Bright's Disease characterized by prolonged widespread nephrotic oedema, compensated renal function, and, in the early stages, by an absence of hypertension and cardiovascular hypertrophy.

Etiology: Commonly, no cause for the disease can be discovered. Occasionally, a history of acute nephritis many years before is obtainable. Not infrequently, an attack of scarlet fever, with or without haematuria, will be remembered. It is probable that most of these cases are the direct expression of a low-grade smouldering inflammation of the kidneys caused by the ordinary common cold or influenzal attack to which man is so frequently subject.

Pathological Changes. Macroscopic: The kidneys are enlarged and oedematous and are typically of the "large white" variety. The capsule strips readily and exposes a smooth, or finely granular, straw-coloured, or grayish-white, surface studded with closely-packed lipoid flecks. Petechial haemorrhages are rarely present and, in their absence, this kidney macroscopically cannot be differentiated with certainty from the large white kidney of chronic nephrosis.

The cortical pattern is blurred and is poorly demarcated from the medulla. Lipoid is seen as opaque yellow streaks in the medullary pyramids. In the later stages, the arteries in the intermediate zone are more prominent than in normal specimens.

Microscopic: The outstanding glomerular change in this group is the degree of proliferative glomerulitis. Proliferative capsulitis is also present, but is a less conspicuous feature. The degree of proliferative glomerulitis present is greater in these kidneys than in any other form of Bright's Disease. The rare glomerular tuft shows fibroblastic invasion and glomerular destruction. Apart from the proliferative glomerulitis, however, the glomeruli appear typically to be intact and there is very little evidence of progressive glomerular destruction. Lipoid degeneration of the capsular epithelium is present in most examples and hyaline-droplet degeneration is absent.

The tubular epithelium is conspicuous by the marked degree of lipoid degeneration and the absence of hyaline-droplet degeneration. Red cells and neutrophilic leucocytes are less abundant in the lumina of the tubules, while desquamated epithelial cells and lipoid casts are more abundant.

The interstitial tissue is diffusely in-

creased, although not as uniformly as in subacute nephritis. The fibrosis is characteristically peri-glomerular with accompanying regional tubular atrophy. Between these areas, the fibrosis is much less dense and encloses numbers of dilated tubules with flattened epithelial cells. The areas of atrophic tubules enclosed in fibrous tissue, alternating with those of dilated tubules in a loose stroma, are very striking. Conspicuous groups of foam cells laden with lipoid are present in the interstitium in all cases.

The arteries and arterioles of these kidneys show medial hypertrophy of variable degree.

Chemical Pathology: The chemical pathology is the same as that of chronic nephrosis until renal insufficiency appears, when the finding of nitrogen retention is added to the characteristic lipoid and serum protein changes of nephrosis.

Clinical Picture: Subchronic nephritis occurs in both sexes and over a span of age from fifteen to sixty. Commonly, it is observed in the forties, though Russell found the average age of the group she studied to be twenty-six.

The illness begins insidiously with oedema of the face and legs. These patients have been described well as those with pale puffy faces and pale white kidneys. It is common to observe this onset shortly after an acute upper-respiratory infection, and to find small numbers of red-blood cells in the urine. A state of progressive widespread oedema associated with nausea, vomiting and abdominal pain may force the patient to his bed. More often, for a time they continue their work in a state of chronic ill health. These are the nephritics with signs but few symptoms. The pale countenance may be a reflection of a true anaemia, but is more often an expression of oedema. At first, renal function is intact and tests of renal efficiency show good concentrating power of the kidneys and normal figures for the blood N.P.N. Later, however, these patients begin to suffer from nycturia with an obligatory polyuria. They are then in a state of compensated renal function and are able to get rid of the nitrogenous waste products by the excretion of an increasing volume of water. It is important to emphasize that, in these casese as in nephrosis, there is no inability of the kidneys to excrete salt and water brought to them. The salt and water are pre-renally deviated to the tissues on account of the low-colloid osmotic pressure of the blood. As in nephrosis, this low colloid osmotic pressure is produced by the heavy albuminuria and resultant fall in the serum proteins. Towards the end of this stage of nephritis, the destruction of renal tissue becomes so great that scarring and fibrosis appear to stop or decrease greatly the loss of albumin. This change is reflected by a rise in serum osmotic pressure and a disappearance of the nephrotic oedema.

As the disease progresses from early to middle and late stages, evidence of cardio-vascular damage appears. These patients begin to suffer from headaches and breathlessness on effort. Examination then reveals slight to moderately elevated blood pressure with figures around 160/94. The fundus oculi may reveal early arterio-sclerotic changes in the vessels and a wet oedematous retina. A fair proportion pass into the stage of chronic nephritis, presently to be described, and die a uraemic death. This outcome is especially apt to occur in the event of an acute exacerbation following an intercurrent upper-respiratory infection.

More often, a secondary infection, such as bronchopneumonia, causes the death of

the patient. Oedema of the lungs, due to cardiac failure, and acute peritonitis with ascites are other forms of termination of this disease.

It is important to stress the close clinical resemblance of this disease to chronic nephrosis. It is so close that in the early stages it may be impossible to tell them apart. There are those who believe that no such disease as chronic nephrosis exists and that such cases are, in fact, cases of subchronic nephritis with nephrotic oedema.

Differential Diagnosis: Chronic nephrosis is differentiated from subchronic nephritis by the lack of any history of acute nephritis, and by the absence of haematuria at any stage. The distinction may be made only by the passage of time when such features as haematuria, hypertension, slight cardiac hypertrophy, early retinal changes, and impaired renal function tests point to the existence of subchronic nephritis. Should the patient die of an intercurrent infection before these changes occur, the only way to distinguish nephrosis from subchronic nephritis would be by the microscopic appearances of the kidneys described above, at post-mortem examination.

Treatment: It is essential to protect the patient from acute exacerbations by removing all foci of infection, such as diseased tonsils and teeth, and by careful supervision of environmental conditions. The dietary management is the same as that of nephrosis, until nitrogen retention begins to appear. At that point it will be necessary to restrict protein in accordance with the method described for acute nephritis. Anaemia is treated by iron therapy and the state of lowered metabolism by the administration of thyroid extract.

4. *Chronic Diffuse Glomerulo-Nephritis (Chronic Interstitial Nephritis, Chronic Azotaemic Nephritis, Third Stage Glomerulo-Nephritis, Chronic Toxic Nephritis, Chronic Nephritis without Oedema, Secondary Contracted Kidney)*

Definition: An end-stage form of Chronic Bright's Disease, characterized by absence of oedema and by the presence of nitrogen retention and, usually, also by cardiovascular hypertrophy and hypertension.

Etiology: It is believed that all of these cases arise from an antecedent attack of acute nephritis at some time in the past. Many of them have gone through the stage of subchronic nephritis to terminate in this form of the disease.

Pathological Changes. Macroscopic: The kidneys are known as secondarily-contracted kidneys. They are variable in size, firm to the touch, pale straw or gray in colour, and possess a thickened capsule that is stripped with difficulty. The exposed surface is finely granular, due to a diffuse fibrotic scarring, with intervening islands of hypertrophied nephrons. A variable degree of contraction results in kidneys that may be normal in size or so small as to weigh together but 75 grams. The cut surface presents a narrowed irregular cortex, so thin in places that the medullary pyramids almost reach the surface. The cortical markings are obliterated and demarcation from the medulla is blurred. Large portions of the cortex are replaced by a scattered meshwork of fibrosis. Yellowish streaks of lipoid are noted in the medullary pyramids, and marked thickening of the renal vessels is present in all cases where hypertension had been present for some time before death.

Microscopic: The glomeruli show a

striking degree of proliferative glomerulitis which involves all the surviving glomeruli uniformly. Many of these glomeruli have reached the late stage of proliferative glomerulitis that is characterized by hyaline necrosis of the tufts. A variable degree of proliferative capsulitis is present. Adhesions between the tufts and Bowman's capsule are commonly found but are not conspicuous. Only a relatively small number of glomeruli disappear in consequence of complete destruction.

The tubular changes are those of atrophy and hypertrophy. Those tubules which drain the filtrate from badly damaged glomeruli undergo atrophy and a replacement fibrosis. The tubules of relatively undamaged intervening nephrons undergo hypertrophy. The tubular epithelium shows great albuminous, and occasionally hyaline-droplet, degeneration. The lumina contain neutrophilic leucocytes and variable numbers of red cells, granular and hyaline casts.

Fibrosis of the interstitial tissue is diffuse throughout both kidneys. This increase in scar tissue is not entirely uniform, for there may be seen areas of denser fibrosis enclosing atrophied tubules and small islands of less dense fibrosis enclosing dilated tubules. A diffuse dense infiltration with inflammatory cells is present in the interstitium. It consists of lymphocytes, plasma cells, and a moderate number of neutrophil leucocytes. A large amount of lipoid is contained within form cells which lie in columns between the loops of Henle.

Cardiovascular hypertrophy may be slight, moderate or great, depending on the degree of pre-existent hypertension. Fatty hyaline degeneration is constantly present in a few of the vasa afferentia, and a variable degree of ischaemic glomerular atrophy may be seen.

Chemical Pathology: The outstanding changes that occur in the blood are a rising blood urea and creatinine and a falling serum calcium—in other words, the changes of renal insufficiency and true uraemia.

Clinical Picture: Chronic diffuse nephritis is most commonly encountered in young and middle-aged people before they have lived long enough to develop the arteriosclerotic changes of old age. There is no special sex incidence. Two main divisions of chronic nephritis are encountered: those cases with a maximum degree of hypertension and a minimum degree of renal insufficiency, and those with a minimum degree of hypertension and a maximum of renal insufficiency. Between these two extremes, the majority of cases of chronic nephritis present a mixed picture of both renal insufficiency and hypertension. A common history to obtain is that of antecedent protracted oedema that has since disappeared and has been followed by a period of tiredness and chronic ill health, leading to the condition presently to be described.

The patient of the predominantly hypertensive type consults the doctor because of tiredness, loss of weight, morning headaches, irritability, dizziness, visual disturbances, and shortness of breath on exertion. Occasionally, he may complain of attacks of nocturnal dyspnoea and of swelling of the ankles. Commonly, he has been told he is pale and does not look well.

On examination, these patients are characteristically thin, dehydrated and free of oedema. The ocular fundi show advanced hypertensive neuro-retinopathy with pale optic discs. The left ventricle of the heart is greatly enlarged and gallop rhythm may be present. The mitral first

and aortic second sounds are accentuated. The peripheral arteries are thickened and tortuous. If left ventricular failure be present, there may be rales at the bases of the lungs or even greater degrees of pulmonary oedema. Dependent cardiac oedema is present in some cases. The blood pressure is extremely elevated, being as high as 234/120. These patients are prone to have attacks of hypertensive encephalopathy when they develop terrifying convulsive attacks with extremely high blood and cerebrospinal fluid pressure. The patient may die in one of these attacks which used to be called pseudo-uraemia. A moderate degree of secondary anaemia is usually present.

These cases all show a mild or moderate degree of renal failure with N.P.N. levels of 70 to 80 mg. per 100 c.c. The urine has a low fixed specific gravity of about 1012 and there is an obligatory polyuria and nycturia. The urine contains a small amount of albumin, numerous hyaline and waxy casts, and little or no blood unless there is an acute exacerbation. They are apt to die of cerebral haemorrhage, cardiac failure, or cardiac infarction.

The chronic nephritic of the uraemic type presents a different picture. The story is one of progressive asthenia, anorexia, pallor and loss of weight. The patient is irritable and often drowsy and listless. He is very thirsty and complains of having to void large quantities of urine frequently both day and night. On examination, dehydration and rather marked anaemia are found. The ocular fundi may show nothing but retinal arteriosclerosis. A slight or moderate degree of hypertension and cardiovascular hypertrophy is found. Characteristically, one finds a very high N.P.N. of say 200 mg. per 100 c.c., a creatinine of 5 mg. and a blood calcium of 9 mg. per 100 c.c. The urine is of low specific gravity, 1008 or 1010, while the two-hour and other renal-function tests show great impairment of renal function.

These patients gradually become so weak that they are forced to bed and pass gradually into a state of true uraemia. At this time there may appear a pericardial friction which should always be searched for. They pass into a state of drowsiness, stupor, and finally coma, characterized by deep Kussmaul breathing with marked acidosis and a low CO_2 combining power of the blood. Muscular twitchings, but not convulsive fits, are characteristic and they finally die of respiratory failure in a state of profound uraemic toxaemia.

Differential Diagnosis: The hypertensive type of chronic diffuse nephritic must be distinguished from the patient in the end stage of essential hypertension. In the absence of a good previous history this distinction may be impossible. In general, however, the nephritic patient is pale and anaemic while the hypertensive is not. The blood pressure in chronic nephritis is high, but not usually as high as in terminal essential hypertension. The hypertensive chronic nephritic is usually younger than the essential hypertensive patient. Lastly, urinary abnormalities and moderate impairment of renal function are far more constant in hypertensive chronic nephritis than in essential hypertension.

The uraemic type of chronic diffuse nephritic can scarcely be confused with anything but the so-called malignant hypertensive. The distinction here, too, may be impossible. The malignant hypertensive patient may likewise die of uraemia, but the history is one of a much more fulminating illness, the degree of hypertension is much higher, and the ophthalmoscopic changes more marked. Cardiac damage is more extensive and

anaemia less marked in the malignant hypertensive than in the uraemic chronic nephritic.

Treatment: In brief, there is no satisfactory treatment of chronic nephritis. The best that can be done is to maintain the renal reserve as long as possible by a low-protein high-carbohydrate diet and by allowing a sufficiency of fluid despite the possible development of cardiac oedema. Restlessness and sleeplessness in the early stages may be controlled by the administration of barbiturates. Codeine may be given with aspirin for headache. Cardiac failure is treated by digitalizing the patient. The bowels should be kept free by the use of a saline laxative. Diuretics have no place in the treatment of chronic nephritis. The patient should be kept ambulatory as long as possible, but should be off his feet and resting for at least fourteen out of each twenty-four hours.

The treatment of hypertensive encephalopathy will be described below under the next title. Uraemia is treated by absolute rest in bed and by the administration of a diet of fruit juices and fluid up to 2000 or 3000 c.c. daily. If nausea and vomiting are present, one may administer 1500 or 2000 c.c. of 5% glucose solution intravenously. The muscular twitchings and spasms can be stopped instantly by the slow intravenous administration of 5 c.c. of 10% calcium chloride or gluconate. Eventually, no treatment is of any avail and the patient succumbs.

III. Vascular Bright's Disease

1. *Essential Hypertension (Synonyms: Hyperpiesia, Primarily Contracted Kidney)*

Definition: A disease in which in the early stages, the only detectable physical abnormality is an elevated blood pressure, and in which, in the later stages, cardiovascular hypertrophy and degeneration are predominant. Allbutt defined it as a condition of which a permanently-raised blood pressure is the dominating feature, associated with left-ventricular hypertrophy, terminating usually in heart failure and sometimes in cerebral haemorrhage, and with little evidence of renal insufficiency.

Etiology: The cause of this disease is still unknown. In the beginning it is probably a manifestation of functional hypertonus of the splanchnic arterioles. It is possible that this functional hypertonus first manifests itself in the individual known as a vascular hyper-reactor. This type of patient exhibits a blood pressure that is normal under conditions of ease and elevated under conditions of strain. Only when the blood pressure is consistently elevated is one justified in diagnosing essential hypertension. It seems probable that, after a certain point, the repeated hypertensive insults to the kidney result in a state of partial ischaemia of the afferent glomerular arterioles. Although not proven in man, it appears from the work of Wilson and Byrom that a vicious cycle is established by which the kidney undergoes progressive ischaemic vascular damage. Under these conditions, hypertension is maintained and possibly made worse by the production of renin within the kidneys. It must be emphasized that this chain of events is entirely unproven, but appears likely in the light of recent work. We must not forget that all the changes that occur in hypertension may be the direct result of an initial transient hypertension, but just what causes this initial rise in blood pressure remains a mystery.

Pathological Changes. Macroscopic: The kidney of essential hypertension has

been described as the red—granular, primarily-contracted kidney. Although this is the traditional description, it is a fact that, of Bell and Clawson's series of 420 cases, only 15% had "contracted kidneys" and the majority, in fact, were normal in size. 56% of their cases had smooth kidneys with little naked-eye abnormality, 23% showed fine pitting of the surface, and 21% had a finely granular surface. Fishberg describes it as the arteriolosclerotic kidney with the following characteristics: a usually adherent capsule but not always so, a variable degree of contraction, usually less marked than in the kidney of chronic nephritis, and a granular surface that may be coarse or fine. On section, the kidney is firm and tough. The cortex is thin and poorly demarcated from the medulla. The cortical markings are obscured and irregular scarred areas descend into the medulla from the fibrotic depressions on the surface. The arteries of the intermediate zone are enlarged, abnormally prominent, thickened, and rigid.

Microscopic: Ischaemic glomerular atrophy is the outstanding characteristic of these kidneys. The glomeruli are not uniformly involved in the ischaemic process and a variable number appear normal. When ischaemic atrophy is advanced, the surviving glomeruli are often slightly hypertrophied. All stages of ischaemic glomerular atrophy may be encountered and the glomeruli so found tend to be grouped in foci throughout the cortex either in wedge-shaped areas beneath the renal capsule or in radiating streaks along the course of the interlobular vessels and their branches. In advanced stages, these streaks form an anastomosing network throughout the cortex with intervening areas of normal parenchyma.

The process by which ischaemic glomerular atrophy occurs is roughly as follows:

The first change is a collagenous thickening of the basement membrane of Bowman's capsule at the pole opposite the glomerular hilum. A collagenous crescent is then formed in this region, bounded externally by the thickened basement membrane and internally by the unchanged parietal epithelium. The collagenous fibrils of the crescent coalesce to form a dense demilune stained deep red with Van Gieson's stain. At first, the tuft appears normal and filled with blood, but as the collagenous crescent forms, the glomerulus begins to shrink. The endothelial cells of the tuft disappear gradually with collapse of the capillary lumina, but the capillaries of the hilum remain patent until atrophy is very advanced. At this stage the thick collagenous crescent is now in contact with the periphery of the tuft. The final stage is one of distortion and disintegration in which the fibrous crescent is broken into segments and the intervening gaps invaded by small lymphocytes. The tuft disappears entirely so that all that remains are crescentic laminated areas of collagen lying amongst collections of lymphocytes in the peripheral parts of the cortex. In short, this entire process is one of gradual infarction of the glomerulus by obstructing the afferent arteriole that supplies it, a process of "ischaemic atrophy".

Accompanying the glomerular atrophy, the neighboring tubules also undergo severe atrophy, usually considerably in advance of that present in the neighboring glomeruli. The epithelial cells of the atrophic tubules undergo fatty degenration and their lumina contain fatty or hyaline casts. The non-atrophied tubules show albuminous degeneration.

Associated with the glomerular and

tubular atrophy is a dense focal hyaline fibrosis of the interstitial tissue. The fibrosis is composed of thick collagenous fibrils that seem to begin with a thickening of the basement membrane around the atrophied tubules. Sometimes these fibrotic areas are remarkably free from infiltration; in other instances, especially below the capsule, there is a dense infiltration with small lymphocytes and occasional plasma cells. No lipoid occurs in the interstitial tissue.

Arterial degeneration is a constant finding in these kidneys. The media of the interlobar, arcuate and interlobular arteries is hypertrophied. The intima is also hypertrophied. The most important and constant vascular change is a hyaline degeneration and occlusion of the lumina of the vasa afferentia of the glomeruli and the arteriolae rectae virae. This degeneration is secondary to hypertrophy of the media and intima of these vessels. In most instances, there is, in addition, fibrous degeneration of the hypertrophied media and intima of the larger arteries. The interlobular arteries undergo fatty degeneration.

Space does not permit of a discussion of the pathological changes elsewhere in the body. Hypertrophy of the left ventricle of the heart and of the muscular arteries throughout the body is the usual finding. As most of these cases die of cerebral haemorrhage or of cardiac failure, the usual pathological findings of these conditions are encountered.

Chemical Pathology: The blood of the hypertensive patient commonly shows no abnormalities. Page, however, has been able to demonstrate recently the presence of a pressor substance resembling angiotonin in the blood of hypertensive patients. When heart failure complicates the picture, the blood N.P.N. will likely be elevated moderately.

Clinical Picture: The symptoms and signs of essential hypertension are conveniently described according to the manner in which they affect the different systems of the body. At first, of course, there are no symptoms, but sooner or later these appear in an insidious manner. The disease affects those in the age group of 40 to 60.

The patient may consult the doctor because of attacks of dizziness and buzzing in the ears. Often he complains of visual disturbances such as transient blindness and flashing lights before his eyes. Morning headache that awakens him at 4 a.m. is a common symptom. One day he may notice that an arm or leg becomes suddenly numb, tingling and weak. He may collapse suddenly on the floor with a transient paresis of one leg. Irritability, sleeplessness, and loss of power of mental concentration are very characteristic. Such a patient may one day go into a convulsive state of hyptertensive encephalopathy as described under chronic hypertensive diffuse glomerulo-nephritis. The usual outcome is massive cerebral haemorrhage, coma and death. A few live for a time following a hemiplegia caused by cerebral haemorrhage, but sooner or later another haemorrhage carries them away.

The heart is commonly affected and may be the first vital organ to fail. The hypertensive patient begins to complain of shortness of breath on exertion that becomes slowly and progressively worse. Attacks of paroxysmal nocturnal dyspnoea and pulmonary oedema may occur. Physical examination commonly reveals an elevated blood pressure of say 180/100, enlargement of the left ventricle of the heart, and rales at the bases of the lungs.

The right ventricle also may give way with the resulting development of venous engorgement, enlargement of the liver, ascites and massive oedema. In the end stages, one commonly finds a gallop rhythm of the heart and a patient with total cardiac failure. Cardiac infarction is a not-uncommon occurrence in these patients, being about twice as common as in the non-hypertensives of the same age group.

It is a paradox that, although post-mortem the kidneys always show changes in the afferent arterioles to the glomeruli, yet clinically very few die of uraemia. Only about 8.16% die a uraemic death, and it is likely that when this event occurs the termination is due to the development of "malignant" hypertension. Usually, there are no symptoms of renal inefficiency and few urinary abnormalities unless heart failure be present. The only common renal abnormality that could be attributed to the hypertensive changes in the kidney is the occasional excretion of a trace of albumin. Page, however, claims that, if sufficient care be taken, it is possible to demonstrate an early failure of hypertensives to maintain the renal blood flow and to concentrate the urine.

Lastly, mention must be made of the ocular fundus. Ophthalmoscopic examination commonly reveals a state of retinal arteriosclerosis only. When hypertensive neuro-retinopathy appears, one considers that the patient has entered the malignant phase of the disease.

Differential Diagnosis: This subject has been discussed above under hypertensive chronic diffuse glomerulo-nephritis, to which the reader is referred.

Prognosis: The ultimate outlook is uniformly bad, yet many hypertensive patients live for years even after a cerebral haemorrhage. Bell and Clawson found that, in their series of 420 patients, 187 died of congestive heart failure, 67 of coronary disease, 81 of cerebral haemorrhage and thrombosis, 49 of accident and intercurrent disease, and 36 of renal insufficiency. Christian's and Janeway's figures are in accord with the above.

Treatment: There is as yet no satisfactory treatment for essential hypertension. Recently, anti-pressor renal extracts have been used in the treatment of hypertension, but have not as yet reached the stage of accepted therapy. Until we know the cause of essential hypertension, it is probable that we shall not find the cure. Short of a cure, the best we can do is to regulate the patient's life according to the rule of moderation in all things. It is very important, if possible, to avoid worry and nervous strain. The judicious use of sedatives in the treatment of headache, dizziness, and sleeplessness is important. Cerebral haemorrhage and cardiac failure are treated as they arise, in the usual way. Attacks of hypertensive encephalopathy are treated by venesection and, if necessary, lumbar puncture. At the same time, an intravenous injection of 50 c.c. of 50% sucrose or glucose is indicated. The general plan is to protect the patient from extremes of all kinds, to insist on extra rest, to reduce weight if overweight, and to treat symptoms and complications as they arise.

2. *Malignant Hypertension*

Definition: A clinical syndrome characterized by the rapid development of extremely high blood pressure, fulminating cardio-vascular hypertrophy and degeneration, and the terminal appearance of acutely progressive renal insufficiency.

Etiology: The cause of this syndrome is unknown, but it appears that it may arise in the following ways:

(*a*) De novo, in a short period of six months to a year in a previously healthy individual.
(*b*) As a terminal event in essential hypertension.
(*c*) As a terminal event in chronic diffuse nephritis.
(*d*) As a terminal event in chronic pyelonephritis.
(*e*) As a terminal event in eclamptic toxaemia.

Pathological Changes. Macroscopic: The kidney is moderately contracted with a capsule that is adherent to an even granular outer surface. The colour varies from grayish pink to reddish purple, according to the degree of congestion. The cortex is uniformly narrow and the normal pattern is replaced by anastomosing strands of gray fibrous tissue. When the kidney is congested, the glomeruli appear as pinhead red dots. The demarcation between cortex and medulla is very blurred. The arteries are very prominent. In some cases the surface of the kidney is studded with small haemorrhagic areas.

Microscopic: A considerable number of the glomeruli appear to be normal while a minority are completely disorganized. Proliferative glomerulitis is absent while occasional slight proliferative capsulitis may be found. Adhesive glomerulitis and focal necrosis are constantly present. Ischaemic glomerular atrophy is always present and conspicuous and predominates over toxic glomerular changes. There is reason to believe that this ischaemic glomerular atrophy really represents a relatively acute infarction of the affected glomeruli and that it is due to the characteristic change that occurs in the corresponding afferent arterioles, namely of acute necrosis and fatty hyaline degeneration.

The interstitial tissue undergoes a process of patchy recticular fibrosis. Large trabeculae of dense fibrous tissue contain within their collagenous fibres groups of greatly atrophied tubules. Between these trabeculae lie large islands of tubules that are either normal or show a regenerative hypertrophy. Inflamatory infiltration of the interstitium is sparse and is more focally distributed. The predominant cell is the small lymphocyte, although an occasional plasma cell and neutrophil may be seen.

The tubular epithelium undergoes albuminous and occasionally hyaline-droplet degeneration. The lumina contain a moderate number of red cells and collections of neutrophiles.

The vascular changes in the cortex are striking. Both media and intima of the arteries and arterioles are greatly hypertrophied. The larger arteries show secondary fibrotic degeneration of these coats. The vasa afferentia, as described above, are often obliterated as the sequel of necrosis and fatty hyaline degeneration of their walls.

Other Pathological Changes: Very marked cardio-vascular hypertrophy is a constant finding in these cases. The left ventricle of the heart is very thick and all muscular arteries show marked medial hypertrophy. Degeneration of the arterioles is found also microscopically in the spleen, pancreas, liver, brain, gastro-intestinal tract, and myocardium. Kernohan, Anderson, and Keith found medial hypertrophy of the arterioles of the voluntary muscles.

Chemical Pathology: The blood of these patients shows the characteristic chemical changes of renal insufficiency progressing rapidly to those of true uraemia.

Clinical Picture: These patients are usually men in their forties and, as stated

above, they are subject to a rapidly progressive fatal disease in which very high blood pressure, cardiac embarrassment, and renal failure are the characteristic features. Reference has been made to the manner in which this fatal syndrome may arise. Irrespective of whether it arises de novo or by complicating and terminating some other disease, there can be no mistaking the symptoms. The patient goes downhill very rapidly with the development of great weakness, severe headache, blindness, dyspnoea, and finally uraemia and death. Although the majority of the cases die of renal failure, heart failure sometimes plays a conspicuous and even dominating part in the picture.

The ocular fundi show marked hypertensive neuroretinopathy with papilloedema, retinal haemorrhages, cotton-wool exudates, a macular star and severe degenerative retinal arteriosclerosis. The heart is greatly enlarged and commonly has a gallop rhythm. The blood pressure is extremely elevated to levels approaching 300/180. A variable degree of cardiac failure may be present, but it is usually inconspicuous. Often petechial haemorrhages are noted in the skin. Terminally, the picture is that of uraemic coma as described above.

The urine characteristically has a low fixed specific gravity with moderate albuminuria. Microscopically, red cells, pus cells, hyaline and granular casts are found. Renal function tests invariably show severe impairment of function.

Prognosis: The outlook is hopeless, with death occurring in six months to two years from the onset.

Treatment: There is no treatment that is of any avail in these cases. In a few early cases, splanchnic sympathectomy has been done with temporary improvement—notably in the Mayo Clinic.

IV. Chronic Pyelonephritis

In recent years since the work of Parker and Weiss, we have come to include this disease under Bright's Disease since it can produce both renal insufficiency and hypertension with cardiovascular hypertrophy.

Definition: A chronic ascending non-suppurative inflammation of the interstitium of the kidney which results in fibrosis, hyptertension and renal insufficiency.

Pathological Changes. Macroscopic: In the absence of hydronephrosis which may be present, the kidney is small, granular, and grossly or finely scarred. Each depressed scar represents a healed area of inflammation which resembles an old healed infarct. When the scarring is finer, the kidney may be indistinguishable from that of chronic diffuse nephritis. Both kidneys are commonly involved, but the disease may be confined to one side.

Microscopic: The glomeruli of affected nephrons show focal necrosis, adhesions, and occasionally proliferative capsulitis. A periglomerular fibrosis produces hyalinized glomeruli which may disappear entirely.

The convoluted tubules undergo marked atrophy, while the collecting tubules contain numerous neutrophilic leucocytes.

In the late stages, some of the scarred areas contain groups of greatly dilated tubules with flattened epithelium. The lumina are filled with colloid-like casts so that the tissue resembles thyroid gland. It is probable that these casts represent the fused nuclear material of accumulations of neutrophilic leucocytes. Decreasing numbers of leucocytes are present in the fibrous interstitium which is patchy or moderately uniform in distribution.

The arteries in the scarred areas show intimal hyperplasia with narrowing of the

lumina. The arterioles show hyperplastic sclerosis with thickening of the entire wall and narrowing of the lumen. The inevitable result of these vascular changes is renal ischaemia and arterial hypertension.

Chemical Pathology: As in former examples of Bright's Disease, renal failure may occur with resulting nitrogen retention. More often, there is no chemical abnormality.

Clinical Picture: The usual story of these patients is that of an antecedent attack of acute pyelonephritis at some time in the past and the subsequent development of hypertension. Occasionally, they may be discovered by the occurrence of urinary frequency and the finding of albuminuria and pyuria. It may be almost impossible to distinguish them from patients with chronic diffuse glomerulo-nephritis. Usually radiological investigation by means of pyelograms is necessary to establish a clinical diagnosis. A marked radiological abnormality in one or both kidneys is of assistance in establishing the diagnosis. The usual symptoms and physical signs of hypertension and renal failure may occur in these as in other forms of Bright's Disease.

Prognosis: If the disease is unilateral, the prognosis is good, for the diseased kidney can be removed by the surgeon. If the disease is bilateral, the prognosis is the same as that of chronic diffuse glomerulo-nephritis, i.e. poor.

Differential Diagnosis: The disease must be differentiated from chronic diffuse glomerulo-nephritis and essential hypertension. The distinction may be very difficult but is made on the characteristic histories and the radiological findings.

Treatment: If the disease is unilateral, nephrectomy is performed; if bilateral, the treatment is that of chronic diffuse glomerulo-nephritis.

* * *

It will be clear from the foregoing account that Bright's Disease is an extremely involved and difficult subject. Although much has been learned, much remains still to be discovered. It is probable that all forms of chronic Bright's Disease, in which renal sclerosis occurs, are subject to a vicious cycle which tends to cause progressive deterioration of the patient's condition and death from hypertension with cardio-vascular hypertrophy and degeneration, or from renal insufficiency and uraemia.

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RENAL FUNCTION TESTS AND THEIR INTERPRETATION*

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In the performance of its ordinary functions the kidney is called upon to excrete water, salts, urea, etc., in quantities, which may vary widely from hour to hour, and of which the variations are independent the one of the others. To meet this situation it is necessary that the kidney be able to elaborate at one time a highly concentrated urine (having a specific gravity of perhaps 1.040 or more), and at another one very dilute (with a specific gravity of 1.005 or less). The capacity to bring about such changes of concentration is one of the most striking characteristics of the normal kidney; and a reduction in this capacity is one of the earliest and most easily observed effects of a failure of functional efficiency.

Both the concentrating power of the kidney, and its diluting power are greatly in excess of any ordinary requirement. It is possible therefore for either, or both, to undergo considerable diminution without any evident effect upon either the volume, the specific gravity, or the composition of the urine. In such a state the kidney, so long as it is not subjected to any unusual strain, performs its excretory functions as adequately as ever. Its subnormal capacity will be revealed only by tests which subject it to strain, or which, like the urea clearance test, measure its excretory performance against a normal standard.

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If the loss of concentrating power is progressive, a time will come when the specific gravity of the urine can no longer be raised to that height, which a normal behaviour on occasion might require. In this state of affairs—known as *hyposthenuria*—the urine is of necessity more than normally dilute. In order then to carry the same total amount of solids as before, it is compelled to increase its total volume. The state of hyposthenuria develops therefore into one of *obligatory polyuria*. This polyuria is so far beneficial, that it compensates for the loss of concentrating power, and enables the kidney still to eliminate the daily quota of metabolites. At this stage, therefore, there may not yet be any notable accumulation of waste products in the blood.

As the functional efficiency of the kidney continues to fail, the stages of increasing hyposthenuria and polyuria pass into that of *isosthenuria*. This implies a total loss of concentrating power on the part of the tubules, so that the specific gravity of the urine is now the same as that of the glomerular filtrate, i.e. of deproteinised plasma. The specific gravity is accordingly fixed at the low level of about 1.010, and the volume, still large, varies but little from hour to hour, or as between day and night. *Nycturia*, therefore, becomes a prominent symptom. The kidney is now working continuously at maximum capacity. Even so, it may no longer succeed in clearing the blood of urea and other nitrogenous wastes. The N.P.N. of the blood accordingly begins to rise.

The maintenance of a compensating

polyuria is dependent upon the production of an adequate volume of glomerular filtrate. A continued diminution in the number of functioning glomeruli—i.e. of the available filtering surface—will involve ultimately a diminution in the rate at which water itself can be eliminated. The volume of the urine then begins to fall off again. In the later stages therefore, of chronic glomerulo-nephritis, although the specific gravity of the urine remains low, its volume may be found within ordinary limits—a state of "pseudo-normal-uria". In this state the excretory function of the kidney will be more than ever embarrassed, the N.P.N. of the blood will be correspondingly raised, and the patient will be well on the way to uraemia.

Further failure of glomerular function leads finally to complete, or almost complete, *anuria*.

The Two Hour Test

From the foregoing description it will be evident that many of the qualitative effects of failing function require for their detection no equipment other than a measuring graduate and a specific gravity bulb. The simplest method of testing renal efficiency consists in fact in observing the fluctuations of urinary volume and specific gravity under the ordinary conditions of everyday life. This is best accomplished by following the routine prescribed in the so-called "two-hour test", associated with the name of Mosenthal. In this routine it is not now considered necessary to place the patient under any special restrictions with respect to food, drink, or activity, but it is desirable that no liquid be taken at night, i.e. after 6 p.m. on the day of the test. The bladder is emptied just before breakfast, say at 8 a.m., and the first specimen of urine is collected exactly 2 hours later. Other specimens are taken at every second hour thereafter up to the twelfth hour (8 p.m.). The urine passed during the remaining twelve hours of the twenty-four constitutes the "night urine", and is united into a single specimen. All seven specimens are measured, and the specific gravity of each is determined.

The response of normal kidneys to this routine presents the following features:

(1) At least one of the seven specimens shows a specific gravity of 1.020 or more.

(2) The difference between the maximum specific gravity observed and the lowest is at least 0.009.

(3) The night urine has a volume which does not exceed 725 cc.

The response of abnormal kidneys depends on the nature and degree of the renal damage. In acute nephritis or nephrosis the volume of the excreted urine is diminished and its specific gravity raised. If recovery follows, the discharge of retained water leads to high urine volumes with lowered specific gravities. Under such circumstances the test gives little information of value either in diagnosis or prognosis. Its chief usefulness is in detecting, and following the course of, a chronic glomerulo-nephritis. In this condition the first indications of defective function are a failure of the specific gravity to rise at any time to 1.020, and a diminution in the range of its variations. These indications are usually accompanied by some increase in the volume of the night urine. As renal damage increases, the specific gravity continues to sink, and its variability to diminish, until finally it becomes fixed at 1009 - 1011. At the same time polyuria develops and increases, while the volume of the night

rises to equal or surpass that of the day. In the final stages the urine volume sinks again, but its specific gravity remains low.

The two-hour test tells us how successfully the kidney is meeting the demands actually being made upon it at the time. Apart from the fact that its indications are merely qualitative, its principal deficiencies are (1) that in the earlier stages of a progressive degeneration it gives no information concerning the extent to which the reserve powers of the kidney have already been called into play, and (2) that in the later stages, once the specific gravity has become fixed, it does not reveal the rate at which further deterioration is taking place. With respect to the first of these deficiencies it has been mentioned already that the kidney can tolerate a considerable amount of damage without any evident diminution of its excretory performance. The existence of such early damage, or at later stages the margin of reserve power still available, can be revealed only by tests which place upon the kidneys an extra load. This is the rationale of the *dilution* and *concentration* tests. These —or at least the latter—should be resorted to even when the two-hour test gives a normal response. Of the two the more useful is the concentration test; but, if both are to be employed, the dilution test should be the first to be applied.

The Dilution Test or Water Test

The patient empties his bladder, and during the next twenty minutes drinks 1500 cc. of water. The bladder is emptied again 30 minutes after the beginning of the test, furnishing the first specimen of urine. Later specimens are collected at each succeeding half hour, until eight in all have been obtained. The volume of each is measured, and its specific gravity determined. In addition it is generally useful to measure the total volume of urine passed during the following twenty hours, i.e. up to twenty-four hours from the commencement of the test.

A normal response consists in the excretion of about two-thirds of the ingested water—i.e. 1000 cc.—within the first 90 minutes, and of the whole of it—1500 cc.— within the first three hours. In addition the specific gravity during the diuresis should be decidedly low, dropping possibly to 1002.

In nephrosis and in acute nephritis very little of the water is excreted, most of it being retained as oedema fluid. If oedema exsits already, the test is definitely contra-indicated.

In chronic nephritis the typical response shows (1) a delay in the excretion of the water and (2) a less conspicuous fall in the specific gravity of the urine. These effects will be more or less evident, according as the renal damage is more or less pronounced.

The interpretation of the dilution test in terms of renal structures affected is not entirely simple. The diuresis that follows water drinking is brought about less by an increase in the volume of the glomerular filtrate, than by a diminution in the amount of water reabsorbed from the tubules. The tubules, operating through an increase in the active reabsorption of chlorides, are probably responsible also for the striking fall in specific gravity. At the same time it is evident that water excreted in the urine must first have been filtered through the glomeruli. The speed with which an extra water load can be eliminated is therefore conditioned in the first place by the available area of

filtering surface. To this extent the time required for its elimination stands in inverse relation to the number of still functioning glomeruli. The relative inability of the damaged kidney to lower the specific gravity may be due to a failure in the tubular function of reabsorbing chlorides. However this may be, the water test, taken as a whole, informs us of how great a polyuria the kidney is capable—how far, therefore, it is still able to compensate for lack of concentrating power by an increase in urinary volume. In this respect its value is prognostic rather than diagnostic.

A still more delicate test of renal efficiency, and one yielding in general more consistent results, is the "concentration test".

The Concentration Test

There are several ways of carrying out the concentration test. The following is the procedure recommended by Newburgh.

After an evening meal the patient is instructed to take no fluids until the test has been completed. Solid food is not prohibited, but, if taken at all, must be restricted to items selected for their dryness—such articles, e.g. as bread, dry cereals, butter, heavy cream, dried fruits, sugar, etc. All urine passed up to bed time of the second night is discarded. A sample is collected the following morning, and its specific gravity is determined. Two hours later a second sample is obtained. If the specific gravity of this sample is no higher than that of the first, the test is terminated. Otherwise a third sample, and, if necessary, still others are collected at two hour intervals, until it is clear that the maximum specific gravity attainable by the patient has been reached.

A normal response is a maximum specific gravity of at least 1029. Any maximum lower than this indicates a deficiency of concentrating power. The lower the maximum, the greater the deficiency indicated. A maximum of only 1008 - 1010 demonstrates a practically complete loss of concentrating ability.

While the dilution test affords some measure of the maximum activity of the glomeruli, the concentration test determines essentially the maximum activity of the tubules. It tells us therefore, roughly at least, how far, in comparison with the normal, the function of the tubules has been impaired. It gives earlier and more delicate indications of depressed renal function than the two-hour test. In a general way the extent to which the maximum specific gravity is depressed parallels quite closely the degree of renal inefficiency measured by the much more elaborate urea clearance test. In some conditions it may reveal a definitely substandard efficiency, even when the urea clearance is within normal limits. This has been observed in mild cases of acute nephritis, during recovery from acute nephritis, in some cases of vascular nephritis and in some of nephrosis. Such instances show it to be on the whole the most sensitive of all tests of renal efficiency. It is particularly useful in deciding when recovery from an acute nephritis is really complete. On the other hand, once the concentrating power of the kidney has been lost completely, the test fails to show any further progressive deterioration of the case. A maximum specific gravity of only 1010 is not inconsistent with a urea clearance of as much as 20 - 30%;

while clearances may fall almost to 5% before uraemia becomes imminent.

Blood Analysis

So long as the kidney can compensate by polyuria for a loss of concentrating power, the blood can be cleared of waste products with reasonable efficiency. A very considerable reduction in overall efficiency may therefore be consistent with a practically normal blood chemistry. An accumulation of wastes is inevitable only when the condition of isosthenuria has been reached, and the urea clearance has fallen to about 20 per cent. It may indeed occur earlier, but is hardly ever encountered in cases having a clearance of 50 per cent or more. Blood analysis is therefore seldom of value in the earlier stages of chronic kidney disease. In the advanced stages it may be of use not only in estimating the prognosis at any particular time, but also in following the progress either of deterioration or of recovery. Blood analysis is useful also in charting the course of an acute nephritis or nephrosis.

The blood constituents, upon the accumulation of which it is most usual to place emphasis, are urea, creatinine and the total non-protein nitrogen. Normally these vary within the following limits, the figures representing in each case mgms. per 100 cc.

N.P.N.	23 - 42	Mean 32
Urea	11 - 50	Mean 30
Creatinine	1 - 2	Mean 1.5

(Note: The lowest urea values are found only in women. For men the minimum is about 26 mgms.)

It matters very little whether N.P.N., urea or creatinine is determined. All three accumulate in general in a parallel manner. In the normal, urea contributes about one-half of the total N.P.N. As the latter rises, the urea comes to form a greater percentage of the whole, and this increased percentage has sometimes been thought to be itself a valuable criterion of failing efficiency. Special significance in a prognostic sense has been attached to creatinine; but on the whole a simple determination of blood urea probably furnishes as much information as blood chemistry is capable of supplying.

If the urea clearance (see later) be taken as the best single criterion of renal efficiency, then the range of urea and N.P.N. values that may be associated with functional damage of varying degrees, is indicated in the following table:

Degree of Impairment	*Urea Clearance (percentage)*	*N.P.N.*	*Urea*
Very slight	60	23 - 42	11 - 50
Slight	40	30 - 50	17 - 65
Moderate	20	35 - 90	36 - 120
Severe	10	40 - 150	43 - 240
Very severe	10	60 - 220	85 - 385
Uraemia		up to 350	up to 650

It will be seen that in a general way the urea and total N.P.N. increase with advancing impairment of renal function; but (1) that the increase is not conspicuous until the impairment has become really marked, and (2) that even when the damage is severe the increase, in individual cases, *may* be relatively small. It follows that the result of a single determination may or may not constitute a fair measure of the severity of the case. High values, if not to be accounted for by some extra-renal condition, are always significant; values near to the normal may be quite misleading. The trend of results obtained at successive intervals will of course be more informative than any single examination.

The figures given, and the comments

made, apply particularly to chronic glomerulo-nephritis. In acute nephritis blood urea may be very high, but it subsides as the case improves. In nephrosis nitrogen retention is not a feature, and the urea may be normal even when albuminuria and oedema are severe. It is likely to rise only if the volume of the urine is seriously reduced. With complete anuria it may reach levels as high as those of terminal glomerulo-nephritis.

The Blood Urea Clearance Test

Most of the preceding tests are susceptible of a roughly quantitative interpretation; but in essence they are mainly of qualitative significance. For a truly quantitative estimate of the kidney's excretory capacity one must resort to the blood urea clearance test.

The *blood urea clearance* is defined as that volume of blood which, in the given case, contains the amount of urea excreted by the kidney within one minute. To put it in another way, it is the volume of blood which would be "cleared" of urea in one minute, if the blood gave up all of its urea as it traversed the kidney.

The use of the urea clearance as a measure of renal efficiency is based upon the known laws governing the rate at which the kidney removes urea from the blood.

The chief factors affecting the rate of urea excretion are (1) the concentration of urea in the blood and (2) the rate of formation of the urine, expressible as the urine volume per unit of time. Other factors less continuously operative —e.g. exercise, diuretics, etc.—have an influence difficult to evaluate, but which under properly standardized conditions may be left out of the reckoning.

The influence of the first factor—the blood urea—is expressed in the statement that, *with constant urine volume*, the rate of urea excretion is proportional to the concentration of urea in the blood. The influence of the second is such that, *with constant blood urea*, the rate of urea excretion is proportional to the square root of the urine volume.

In order to express these relations concisely it is convenient to adopt the following symbols. Let

U = the concentration of urea in the urine, say in mgms. per c.c.,

B = the concentration of urea in the blood, in the same units,

and V = the rate of urine formation in cc. per minute (urine volume).

Then the rate of urea excretion, in mgms. per minute, will be UV; and the two statements just made can be formulated as (1) $UV = k_1B$ and (2) $UV = k_2\sqrt{V}$, and can then be combined in the single equation

$$UV = C_1(B \times \sqrt{V}) \ldots . \quad (3)$$

in which C_1 is a complex constant made up of two individual constants of proportionality. Equation (3) can be rearranged as

$$C_1 = \frac{UV}{B\sqrt{V}} \text{ or } C_1 = \frac{U}{B} \times \sqrt{V} . \quad (4)$$

So long as the rate of urine formation, or urine volume (V), is not too great, Equation (3) or (4), it has been found, describes the relations in question with reasonable accuracy. It fails to do so, whenever the urine volume rises above a certain level, known as the "augmentation limit". This limit is reached in different individuals at a rate of from 1.7 to 2.5 cc. of urine per minute, and has an average value of about 2.13. Once it has been attained, the rate of urea excretion becomes independent of the urinary volume. An increase of

the latter no longer "washes out" more urea from the blood, but merely makes the urine more dilute. The rate of urea excretion is then proportional solely to the urea concentration of the blood. In symbols

$$UV = C_2 \times B \quad \ldots\ldots\ldots (5)$$

$$\text{or } C_2 = \frac{U}{B} \times V \quad \ldots\ldots\ldots (6)$$

C_2 being a constant different from C_1.

C_1 and C_2 might be regarded simply as mathematical "constants of urea excretion", applicable respectively to cases where the urinary flow was below or above the augmentation limit. But it is possible to assign to them a more concrete significance. It is evident that in any specific case the quotient $\frac{U}{B}$ will express numerically the number of times urea has been concentrated in passing from blood to urine. In other words 1 cc. of urine contains that amount of urea which was present in $\frac{U}{B}$ cc. of blood. Since V cc. of urine are excreted each minute, $\frac{UV}{B}$ cc. will be the volume of blood, which contains the amount of urea excreted in one minute; and that, by definition is the *blood urea clearance.* This then is the meaning to be assigned to the constant C_2 in equation (5) or (6). It has to be remembered that C_2 *is* a constant only when the rate of urine formation (V) exceeds the augmentation limit of about 2 cc. per minute. At rates falling below this the value of $\frac{UV}{B}$ (the actual or observed clearance) diminishes. The constant clearance attained with high urine volumes is therefore also the *maximum clearance* and is commonly so designated. If it is symbolized as C_m, equation (6) becomes

$$\text{Maximum Blood Urea Clearance} = C_m = \frac{UV}{B},$$

an equation applicable only when V is greater than 2.

For any one individual the maximum clearance has been found to be constant within a probable variation of ± 6 per cent. For different normal adults its mean value varies from about 64 to about 99 cc. For the individual of average adult size the mean maximum clearance is about 75 cc. per minute. This statement means, that with the kidneys working at their hardest the amount of urea excreted per minute is equal to the amount contained in 75 cc. blood. It does not, of course, imply that every minute 75 cc. of blood is *completely* cleared of urea. Actually the blood circulating through the kidney loses only about one half of its urea. On that basis a clearance of 75 cc. would mean that during one minute about 150 cc. of blood had passed through the renal circulation and been subjected to the excreting activity of the kidneys.

To elucidate now the physical significance of the constant C_1 in equation (3) or (4), imagine the case in which V is 1 cc. per minute. Then $\sqrt{V} = V$, and therefore, *in this particular case,* $C_1 = \frac{UV}{B}$. But $\frac{UV}{B}$ is, by definition, the blood urea clearance. C_1 therefore is numerically the blood urea clearance, as it would be, *if the kidneys were producing urine at the rate of 1 cc. per minute.* This rate, conveniently enough, is about the average rate of urine formation for normal adults. It forms therefore a natural standard of reference, and C_1 is accordingly called the "standard clearance", commonly designated C_s. Equation (4) therefore may be written as

Standard blood urea clearance

$$= C_s = \frac{U\sqrt{V}}{B}$$

The mean value of the standard clearance varies in different normal individuals from 40 to 68 cc. of blood per minute, with a probable variation of ± 10 per cent. For adults of average size the range is about 41 to 65 cc. with a mean of 54 cc.

The standard clearance, it must be recognized, is a theoretical magnitude, which will be greater or less than the actual or observed clearance $\frac{(UV)}{B}$ according as the rate of urine formation is less or greater than the standard rate of 1 cc. per minute. Its advantage is that for any pair of kidneys, whether healthy or diseased, it is relatively constant, whereas the actual clearance varies with the urine volume (unless this is in excess of the augmentation limit). The actual clearances of different individuals would be directly comparable only if the urine volume were in each the same—a condition difficult, if not impossible, to fulfill. In the standard clearances we have comparable indices of renal efficiency, readily obtainable without special control of the rate of excretion. Only when the latter exceeds 2 cc. per minute does the calculation of the standard clearance become impossible; but in that case the maximum clearance (which is an actual, not a theoretical magnitude) is available.

A concrete idea of the significance of urea clearances in relation to renal function can be obtained by considering some hypothetical cases. Take, for instance, a normal adult having the average normal standard clearance of 54 cc. per minute. Suppose that his blood urea concentration (B) is 30 mgms. per 100 cc., and suppose further, for simplicity's sake, that he produces urine throughout the day at a constant rate of 1 cc. per minute ($V = 1$). Under these circumstances we can apply the equation

$$\frac{U\sqrt{V}}{B} = C_s,$$

$$\text{i.e.} \quad \frac{U}{30} = 54,$$

$$\text{whence} \quad U = 1620.$$

U (the concentration of urea in the urine) will of course appear in the same terms as B, i.e. mgms. per 100 cc. The urine therefore will contain 1.62 per cent of urea; and since it is formed at the rate of 1 cc. per minute, its total volume in 24 hours will be 1440 cc. The day's output of urea will therefore be 23.3 gms. (The same conclusion can be reached by considering that the 54 cc. of blood cleared each minute contains $\frac{54 \times 30}{100}$ = 16.2 mgms. of urea; the output in 24 hours is therefore 0.162 gms. × 1440 = 23.3 gms.).

Suppose next that the subject's protein metabolism is increased, so that, to maintain nitrogen equilibrium, it is necessary to excrete, say, 33 gms. of urea. This may be accomplished either (1) by increasing the rate of urine formation (V), so that urea is washed out more rapidly from the blood, (2) by increasing the concentration of urea in the blood (B), so that the urinary concentration (U) also rises, or, of course (3) by a combination of both methods.

(1) We have seen, that, with constant blood urea, the rate of urea output (UV) increases as the square root ($\sqrt{V}$) of the urinary volume. Conversely, then, the urinary volume increases as the square of the excretion rate. Now the removal of 33 gms. of urea in the same time as 23.3 gms. means an increase in

excretion rate of 1.416 times. To accomplish this without any rise in the urea concentration of the blood, the urine volume must then be increased $(1.416)^2 = 2$ times, i.e. to 2 cc. per minute, or 2880 cc. per day. This conclusion must, and does, conform to the subject's standard clearance of 54 cc.; for with an output of 33 gms. in 2880 cc. U will be 1146 mgms. per 100 cc.; and since V is now 2, and B is assumed to be, as before, 30, we have

$$C_s = \frac{U\sqrt{V}}{B} = \frac{1146}{30} \times 1.416 = 54.$$

(2) If an output of 33 gms. is to be accomplished with an unaltered urine volume of 1440 cc. ($V = 1$), then the concentration of urea in the urine (U) must obviously be raised to 2290 mgms. per 100 cc. Introducing these values into the equation for standard clearance we have $\frac{2290 \times 1}{B} = 54$, whence $B =$ 42.5. The required output is reached therefore, without increase in urine volume, by raising the blood urea to 42.5 mgms. per 100 cc., which is still within the normal range.

(3) It is evident that the same result could be obtained by many different combinations of urine volume (between 1440 and 2290) and blood urea concentration (between 42.5 and 30). For instance, if the blood urea be raised only to 36, and the daily output only to 2000 cc. (= 1.39 cc. per min.), then we have $U/36 \times \sqrt{1.39} = 54$, whence $U = 1650$ mgms. per 100 cc. The total output of urea is therefore $20 \times$ 1.65 gms. = 33 gms. as before.

Suppose now that, as a consequence of disease, the subject's standard clearance is reduced to one-half of the normal, i.e. to 27 cc. per minute. If urine volume and blood urea remain as at first postulated—i.e. 1440 cc. (or $V = 1$) and 30 mgms.—then it is evident that the output of urea will be reduced to one-half of what it was, i.e. to 11.65 gms. (= 5.45 gms. urea nitrogen). The subject therefore could avoid both polyuria and urea accumulation only by a drastic reduction in protein catabolism.

Imagine, on the other hand, that he doubles the volume of his urine so that $V = 2$. Then, if the blood urea be still maintained at 30, the rate of urea excretion will be increased $\sqrt{2}$ times. The day's output will rise accordingly from 11.65 to 16.5 gms. This is still short of the original 23.3 gms. but represents a substantial advantage gained by polyuria. It should be noted that a still greater polyuria would be of little value; for with $V = 2$, the urine volume would be already at or near the augmentation limit.

Suppose, again, that with the day's volume remaining unaltered at 1440 cc., the blood urea rises to the still normal value of 42.5. The day's output of urea would then rise in proportion, i.e. from 11.65 to $\frac{11.65 \times 42.5}{30} = 16.5$ gms. The same advantage, therefore, would be gained as by doubling the urinary volume.

Let now both compensating factors be brought into play, that is, let a blood urea of 42.5 be combined with a urinary output of 2880 cc. ($V = 2$). Then the equation for standard clearance, gives us

$$\frac{U\sqrt{V}}{B} = C_s,$$

$$\frac{U}{42.5} \times \sqrt{2} = 27,$$

whence $U = 810$,

and the day's output of urea is $28.80 \times$ 810 mgms. = 23.3 gms. This is the output previously attained by the normal kidney with a blood urea of only

30 and a urinary volume of only 1440 cc.

The last calculation shows how it is possible, that kidneys, which have lost 50 per cent of their functional capacity, may hold the blood urea within normal limits, while still excreting as much urea as healthy kidneys. An abnormal increase in the urea or N.P.N. of the blood is in fact a rather late manifestation of kidney damage. It will be the less likely to occur, if the patient whether by choice or direction, is living at a rather low level of protein metablolism.

The urea clearance test may be carried out at any convenient time. No special dietary regime is necessary, but it is best to exclude tea or coffee from the preceding meal and to give the patient a glass of water before commencing the test. At a noted time the bladder is emptied. About 55 minutes later a sample of blood is collected. The bladder is then emptied again, the time noted to the nearest minute, and the volume of the specimen accurately measured. After another exactly noted interval of about one hour, a second urine specimen is secured and measured. The urea concentration of the blood (B) and of each urine specimen (U) is determined, and the rate of urine excretion (V) for each period calculated. B and U must be expressed in the same units, say mgms. per 100 cc. V must always be expressed as cc. per minute. If V is found to exceed 2 cc. per minute one calculates the maximum clearance, $C_m = \frac{UV}{B}$. If V is less than 2 cc. per minute, one calculates the standard clearance $C_s = \frac{U\sqrt{V}}{B}$. In either case it is of advantage then to express the clearance found as a percentage of the average normal, which is 75 for C_m or 54 for C_s. The percentage so calculated signifies percentage of average normal renal efficiency.

In the case of children or of adults differing markedly from the normal size the value found for V should be corrected by multiplying it by the factor $\frac{31.7}{SA}$, where SA is the surface area of the patient in square meters. The calculation of clearance is made with the corrected value of V.

In any given individual, even in one with normal kidneys, both the maximum and the standard clearance are likely to show quite considerable variations. This is because blood urea concentration and urine volume, although they are the chief factors affecting the rate of urea excretion, are not the only ones. For the same reason the range of variation in different normal individuals is rather wide. It is the practice therefore to accept as strictly normal any clearance in excess of 75 per cent. Clearances between 75 per cent and 50 per cent are looked upon as suspicious. A clearance of less than 50 per cent indicates definite impairment of renal function. Accumulation of N.P.N. seldom takes place until the clearance has dropped below 40 per cent, and it may be absent with a clearance of 30 or even 20 %. With clearances below 20% a definitely elevated N.P.N. becomes the rule. Uraemic symptoms are unlikely to appear while the clearance is above 10 per cent, but are practically always present when it falls to about 5 per cent.

Both in nephritis and in nephrosis the fall in blood urea clearance is proportional to glomerular destruction. In the arteriosclerotic type of Bright's disease it appears to be proportional to the arteriolar damage (Van Slyke, Stillman et al., 1930).

Feature Section

THE GRADUATING CLASS

Previous graduating classes have recorded their views from time to time by answering questionaires, and it was decided to follow the precedent with the present sixth year. Accordingly, some seventy answers were received from a class of one hundred and ten, and although we do not pretend to suppose this response is truly representative of the whole year, nevertheless some idea may be had of the trend of class opinion. The questions involved dealt with vital statistics, education and questions relating to medical studies and the practice of medicine.

It was found that age distribution of the class was as follows:

21 years— 6	26 " — 7
22 " —13	27 " — 2
23 " —17	29 " — 2
24 " —13	30 " — 1
25 " — 8	31 " — 1

This suggests a wide age distribution which is probably due to the fact that many students enter medicine after taking other university courses, or after working in other professions.

Another question dealt with the occupation of the members of the class before they began medicine. The answers were illuminating in that seven had taught school, while others had worked in factories, as salesmen, clerks, bookkeepers and labourers. Two had been on the University staff before they began their present course.

A third question dealt with the years interning or post-graduate studies the class anticipated before going into practice, conditions of course permitting. These are summarized thus:

0 years internship or post graduate	— 1
1 " " " " "	— 5
2 " " " " "	—17
3 " " " " "	—30
4 " " " " "	— 8
5 " " " " "	— 8
6 " " " " "	— 0
7 " " " " "	— 1

This is a most wholesome trend, for after all, no medical college expects to put out finished doctors. The number of students who go into practice on graduation is rapidly diminishing. Most students had very modest aspirations regarding their revenue from the first year of practice. On the whole they might be said to be content to "break even".

Ninety per cent. of the class were enrolled in the R.C.A.M.C. and the preferences for the Services were as follows:

Army —27 or 39%
Navy —19 or 27%
Air Force—24 or 34%

This corresponds closely with the choice of the last graduating class—but unfortunately, not with the proportions required by the Services themselves. It is generally understood that the Army absorbs 75%, the Air Force 15% and the Navy only about 10%.

Regarding the class marital status, 60% were single and 10% were married. The remaining 30% were divided in the "marriage on graduation" group (17) and "single for keeps" (3). Probably no graduating medical class has had such a high proportion of married students.

Most of the class had had no other University training. However, twenty-four had taken one or more years apart from medical work.

1 year University—8
2 " " —4
3 " " —0
4 " " —9
5 " " —1
6 " " —2

In other words, over 35% of the class have had one year or more University extra-medical education.

Asked the question "If you had to take University again, would you again choose medicine?"—there was an affirmative answer in only 87% of the replies. Ten per cent. answered frankly in the negative while three per cent. were undecided. Heading the list of preferential courses was engineering, with dentistry, pass arts, law and business in second place.

Upon inquiring into how many of the class were the sons of doctors, fourteen or 20% belonged in this category. But more surprising is the fact that of the seven students who would not take medicine again, five were in the 20% mentioned above. One wonders whether in these cases, medicine was really the course of their own choosing or whether parental influence, family tradition and circumstance had been also keen at play.

Regarding where the class intend to practice, fully 75% announced rural Ontario would absorb them. Of the remainder, 15% selected Toronto or Montreal and the last 10% would practice in U.S.A., England and Russia. Three students selected this latter.

The choice of future practice is always a matter of interest and often of great concern to the student and his teachers. The following selections are at least enlightening:

General Practice — 23 or 33%
Surgery — 15 or 21%

Paediatrics	—	8 or 11%
Internal Medicine	—	7 or 10%
Obstetrics and Gynaecology	—	5
Genito-urinary Surgery	—	3
Orthopedics	—	3
Psychiatry	—	3
Pathology	—	1
Public Health	—	1
Radiology	—	1
Research	—	1
Endocrinology	—	1
Neurology	—	1

The question dealing with views regarding Health Insurance revealed almost universal approval of some scheme operated by the Medical Council of Canada, and only three were against any form of socialized health programs. The suggestion has been made that this whole topic be made the subject for a future paper or symposium.

While it is realized the answers can hardly be said to represent the opinions of the whole class, yet it seems reasonable to observe the trends of thought of nearly seventy per cent. of the sixth year.

MEDICAL SOCIETY NOTES

FINANCIAL STATEMENT

APRIL-DECEMBER, 1942

Balance, as of April 1st	$1,248.25	Medical Journal	$ 800.00
Fees	2,388.00	M.A.A.	1,000.00
Refunds	157.18	Secretary	50.00
1941-2 At-Home	4.00	Graduation Banquet	181.60
M.W.U.A.		Arts and Letters	175.00
Spring Dance	349.50	Society Keys	86.64
Boat Cruise	75.50	At-Home	66.00
Corn Roast	102.10	M.W.A.A.	25.00
At-Home	20.00	M.W.U.A.	125.00
Flashers and Badges	25.50	Spring Dance	296.00
G. Tamblyn Co.	10.00	Boat Cruise	268.13
Incidentals	30.25	Corn Roast	117.59
		Rentals	87.00
Total	$4,410.28	Flashers and Badges	62.64
Debit	4,082.18	Phone	9.00
		Publicity	316.81
		Trips	148.03
		Incidentals	66.66
		C.A.M.S.I.	201.08
Balance	$ 328.10	Total	$4,082.18

Abstracts

Contributors { E. T. French, B. M. Wilson, J. R. Fulton, J. S. Simpson

Total Thyroidectomy in Heart Disease

By Elliott C. Cutler, M.B.

Kansas City Medical Journal, June 1941

Total Thyroidectomy was first proposed in 1932 because both experimental and clinical evidence led to the belief that this procedure would benefit cardiac cases.

From the clinical evidence—Subtotal thyroidectomy had proven beneficial in patients of long-standing hyperthyroidism even in severe cardiac failure, while from experimental evidence the physiological research of Blumgart and his colleagues had shown that the rate of circulation roughly parallels the metabolic rate, i.e., when metabolic rate is elevated there is a co-existing rapid circulation and when metabolism is low, circulation is slow. The metabolic rate seems to be the dominating factor.

In decompensated heart disease the circulation is slowed but the metabolic demands remain normal. It would appear that if the metabolic rate were lowered by thyroidectomy, the two factors, metabolic rate and speed of circulation, might be brought into equilibrium. When this occurred it was hoped that compensation would be present. As an illustration he sites the case of a male, age 43, with hypertensive heart disease accompanied by dyspnoea; substernal distress; ascites and peripheral edema. Total thyroidectomy was performed and the patient returned to work with B.M.R. stabilized at —36 H.R. 60 and vital capacity 2200 cc. He was then given thyroid medication which produced an abrupt rise of B.M.R. and pulse with rapid fall in vital capacity and return of decompensation.

In order to assay the value of the procedure Dr. Cutler conducted a follow-up on patients who had been submitted to this procedure 5 years ago. and of these he has 57 cases. They are divided into two major groups:

(i) Those with intractible Angina Pectoris and

(ii) Those with some form of congestive heart failure not benefited by ordinary medical means, i.e., patients who in the majority of cases were extremely poor risks. Of these, 32 patients were in Angina groups and 25 patients were in Congested Heart Failure groups. Sixteen survived a 5-year period (12 Anginas and 4 Congestive Heart Failure cases).

Of the 41 non-survivors 5 were post-operative deaths of which all but one were due to heart disease and in both groups, when death occurred within the 5 years, heart disease was almost invariably the major eteological agent with only 2 cases dying of pneumonia.

Period of post operative survival: In the Congestive group 50% died in the first year and only 4 survived 5 years, while in the Angina group 50% had died in 4 years and 12 survived 5 years or one-third of total.

However, since the main justification of this procedure is centered in the amount of relief given to individuals, the relief of symptoms were analysed. In the Angina group 50% over the 6 month period showed marked relief and only 2 no relief; of the 12 living 5 years, 8 had marked relief and sustained it. The 4 surviving from Congestive Failure showed sustained relief and the others were definitely improved. Of the rest, 50% showed some benefit.

If you subdivide the group of patients with congestive heart failure, those of rheumatic origin have a somewhat better outlook than those with arteriosclerotic or hypertensive heart disease. But since the survival figures are in accordance with the life expectancy in patients with these disorders it cannot be shown that these patients live a single additional day as a result of total thyroidectomy. Certainly in Chronic Passive Congestion due to arteriosclerotic and hypertensive heart disease the operation has given disappointing results. In Chronic Passive Congestion due to Rheumatic Fever in chosen cases the operation may be beneficial, i.e., in young people with good myocardium and without excessive failure. If, however, to reach compensation the B.M.R. has to be lowered to such an extent as to produce marked myxedema then thyroidectomy is not desirable.

The best results from total thyroidtectomy have been in patients with intractable Angina. But in these cases also it is hard to be sure as you must evaluate a clinical symptom of pain which is difficult. Moreover the disease may undergo natural remissions and exacerbations and such cases teach us to employ caution in ascribing improvement to a given therapeutic measure just because improvement happens to occur shortly after the thyroidectomy.

In his cases, however, the consistency with which all patients showed at least some relief leads him to conclude that the improvement was not accidental. It is particularly encouraging that although nearly all these patients with Angina were over 60, one-third had survived 5 years.

There is no proof that the patient's life is prolonged as Dublin reports a 28% 5 year survival in cases of actual Coronary thrombosis treated medically.

In Cutler's experience myxedema has never offered a serious problem compared to the heart disease. He stabilizes the patient at about —20 with a B.M.R. from time to time and adjustment of dosage to maintain the —20 level.

J.R.F.

The Anti-sulphanilamide Action of Procaine in Vivo

H. L. De Waal and others

Lancet, Dec. 19, 1942

Woods showed in 1940 that one molecule of p-aminobenzoic acid, in vitro, countered 200 to 500 molecules of sulphanilamide. One molecule of procaine, which has a similar chemical structure, counteracted 20 molecules of sulphanilamide in vitro.

The authors used mice to determine this effect in vivo. The minimum lethal dose of hemolytic streptococcus, and the maximum non-toxic dose of procaine combined with 1:50,000 adrenaline and an aqueous solution of sulphanilamide were used.

In these mice it was found that repeated large doses of procaine which produced a concentration of 0.03 mgm/gm of body weight inhibited the bacteriostatic action of sulphanilamide in a concentration of 32 mgm per 100 c.c. of blood. In

a man of 70 kgm, by analogy, 14 c.c. of a 3% solution will inhibit a blood level of 6 mgms % (or 14 c.c. 1% solution inhibiting a blood level of 2 mgms %, etc.)

The anti-sulphanilamide action is weak or absent if the sulphanilamide has been given for 24 hours before the procaine is given. By then the bacteria are firmly linked by enzyme chains to the sulphonamide, and some natural immunity has had time to develop.

Three human cases are presented in which sulphonamides, and, after some delay, procaine were used in the treatment. All recovered without any, or with only slight delay.

The authors suggest that large doses of procaine and allied anaesthetics ('Larocaine', 'Tutocaine', 'Butyn', 'Anaesthesin', and 'Orthoform') similar to p-aminobenzoic acid, should not be used early in sulphonamide treatment, especially if that treatment is weak or sporadic.

B.M.W.

The Mysterious Mixed Tumors of the Salivary Glands

Joseph McFarland, M.D., Sc.D.

Surgery, Gyn. and Obs., Jan., 1943

Dr. McFarland in this article attempts to correlate and decipher the at present muddled views regarding the pathology of these tumors.

He traces the theories of etiology from the original one of Virchow to those of Krompecher, Cuneo and Veau, and Forgie and Massabau. These workers have been especially interested in the presence of cartilage in these tumors and most authors at present agree with Enrich that the cartilage arises from mucoid degeneration of the epithelial cells of the tumors.

The author claims that these tumors, contrary to popular opinion, are very rare. In his series he found that the interstitial type were three times as frequent as the parenchymatous type but recur less frequently. Regarding the malignancy of these tumors Dr. McFarland states that they are not infiltrative except if trauma or the surgeon breaks their capsule; there is little local tissue destruction; metastases are uncommn and then only in the lymph nodes; however in his series there was roughly 50% recurrence and the smaller the tumor at operation the more likely it is to recur; they interfere with function only when they interefer with the V and VII Nerves or with jaw movement; they exert no general toxic action.

Dr. McFarland finds that the only treatment is complete surgical removal and this should only be done when the tumor is as large as a lemon or interferes with jaw movement or cranial Nerves.

He concludes that microscopic study will not determine danger of recurrence and no surgeon can be completely sure that any tumor he has removed will not recur.

J.S.S.

Treatment of Small Bowel Obstruction

Clarence Dennis, M.D. and
Schuyer P. Brown, M. D.

Surgery, Jan., 1943

The authors prelude their remarks on treatment by a discussion of:

Mechanisms of obstruction, which occur in their experience in the following order of frequency — external hernia, intussusception, adhesive bands, adhesions of the bowel to other structures with the formation of kinks which render the obstruction ever more complete as the degree of distention increases, obturation, volvulus, internal hernia, mesenteric vascular occulsion, and neoplasms.

Manner of onset of symptoms and signs, inculding—pain and cramps produced by either rapid stretching of intestinal muscle or resistance to strong peristaltic contractions of the layer; borborygmus, resulting from propulsion by a peristaltic rush of fluid and gas into an area of increased intraluminar tension; vomiting, consequent to antiperistalsis, faecal vomiting appearing in complete ileal obstruction in two to three days; x-ray signs reveal a ladderlike arrangement of gas filled coils, the ratio of fluid to gas increasing with the duration of the obstruction; shock may make its appearance in unrelieved strangulating obstructions due to outpouring of blood into the lumen of the devitalized gut; back pain occuring in strangulating obstructions due to tension on the mesentery as the gut passes into a hernial orifice; peritoneal irritation, seepage from gangrenous gut resulting in muscle spasm, rebound tenderness, and followed by a rise in temperature and white count; palpable loops which are due to a compensatory hypertrophy of the intestinal muscle in incomplete obstruction, taking seven to ten days to develop.

Causes of death in intestinal obstruction—in high obstruction: dehydration, hypochloraemia, alklosis, and uraemia. In low obstruction: prolonged distention, causing reduced viability of the wall and transmigration of toxins, or possibly lethal affect of afferent nerve impulses; in strangulating obstructions, gangrene of the bowel with resultant shock or peritonitis.

The treatment of small bowel obstruction comprises: (1) The restoration of the patient's water and mineral balance and of his blood pressure to normal; (2) Relief of distention by intubation of the small bowel or by removal of the obstructing mechanism; (3) Resection of such gangrenous bowel as may be present.

Metabolism—The authors employ 20 per cent dextrose solution administered at a rate not faster than 150 c.c. per hour, to satisfy caloric requirements. A proper level of plasma electrolytes and blood urea nitrogen is attained by giving sufficient salt and water to permit excretion of a liter of urine and 2 to 5 Gm. of salt daily. The available vitamins are given parenterally. In patients unable to take food by mouth over a considerable period, the use of amino acid preparations and small amounts of human plasma such as 100 c.c. daily, have become routine in an attempt to maintain a normal nitrogen balance, if plasma protein level is low larger quantities are given.

Intubation — The universal use of Wagensteen or Miller-Abbott siphon suction apparatus in the relief of distention is well known. It is thought desirable in cases seen within forty-eight hours of the onset of symptoms to operate prior to the advent of distention.

Operative procedures—The patient is watched closely at four to six hour intervals for evidences of peritoneal irritation or failure of decompression. Scout films of the abdomen are made from time to time. If a tube cannot be passed into the small bowel in forty-eight hours or if the passage of the tube is not followed by satisfactory decompression a catheter enterostomy is done. If this is not followed by releting of the obstruction exploration is undertaken. In the presence of peritoneal irritation exploratory laparotomy is commenced irregardless of the degree of distention.

Oxygen—High concentrations of oxygen are occasionally used as an adjunct to suction which is not quite adequate.

Results—

For the period '31-'38

patient mortality 17.9%

For the period '38-'40	
patient mortality	19.3
For the period '40-'42	
patient mortality	11.32
Early operation—	
within 24 hours	7.8%
within 48 hours	10
over 48 hours	20

E.T.F.

Conservatism in the Surgical Management of Acute Regional Enteritis

H. G. Smithy, M.D.
Surgery, Jan., 1943

The author reviews five cases of acute regional enteritis which he handled by exploration and appendectomy. All five of these cases showed definite regression during the next month after operation. There is a strong tendency to spontaneous healing in acute regional enteritis which the author illustrates with a case in which there was perforation of the cecum and healing and regression took place spontaneously.

He points out that in those cases in which the greater part of the bowel is involved, operation is impossible and conservatism shows good results.

Very few cases of acute regional enteritis become chronic, most of them clearing up spontaneously when treated conservatively. Also when treated conservatively under observations those cases which do become chronic can be picked up by frequent X-ray study and careful preoperative management carried out which would include transfusions and external chemotherapy as sulphanilyguanidene.

The author always removes the appendix despite the fact that some workers claim it causes fistula formation. If the appendix were not removed it may later become involved in the chronic ganulomatus reaction with appendiceal obstruction and rupture.

J.S.S.

These Books Will Be a Real Help to Any Medical Student

Dorland's "American Illustrated Medical Dictionary"
Beckman's "Treatment in General Practice"
Cecil's "Textbook of Medicine"
Meakins' "Practice of Medicine"
Christopher's "Minor Surgery"
Christopher's "Textbook of Surgery"
Curtis' "Textbook of Gynecology"
Schumann's "Textbook of Obstetrics"
Todd & Sanford's "Clinical Diagnosis by Laboratory Methods"
Griffith & Mitchell's "Textbook of Pediatrics"
Ranson—"Anatomy of the Nervous System"
Pillsbury—"Manual of Dermatology"

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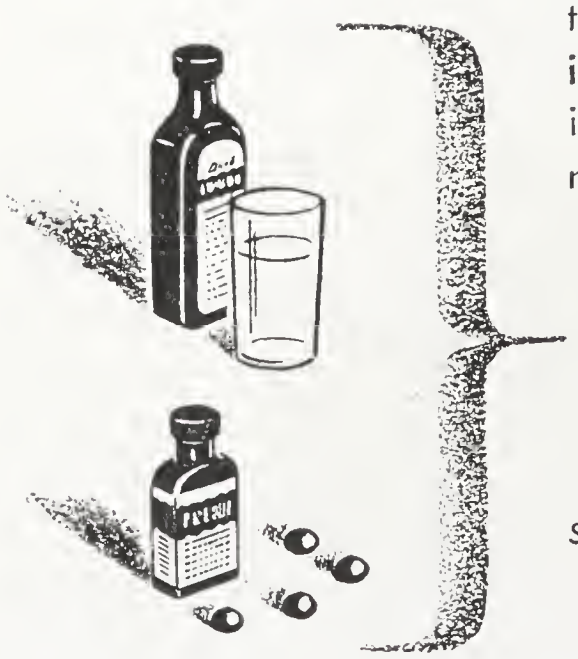

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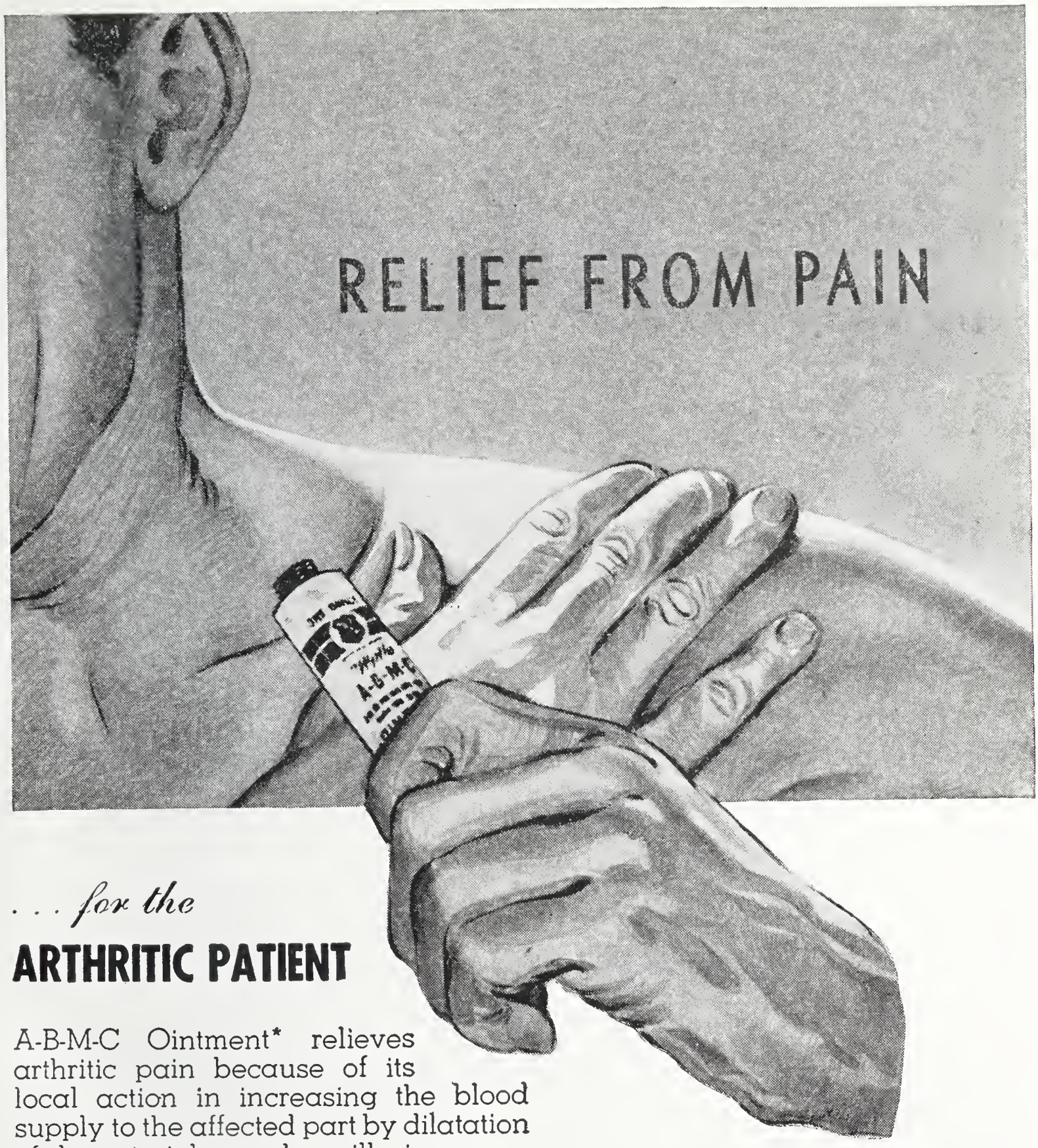

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†Archives of Physical Therapy, *21*, 12 (Jan.) 1940.

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It Can Happen Here

Example of severe rickets in a sunny clime.

LEST WE FORGET—we who are of the vitamin D era—severe rickets is not yet eradicated, and moderate and mild rickets are still prevalent. Here is a white child, supposedly well fed, if judged by weight alone, a farm child apparently living out of doors a good deal. This boy was reared in a section having a latitude between 37° and 42°, where the average amount of fall and winter sunshine is *greater than that in the major portion of Canada*. And yet such stigmata of rickets as *genu varum* and the quadratic head are plain evidence that rickets does occur under these conditions.

How much more likely, then, that rickets will develop among city-bred children who live under a smokepall for a large part of each year. True, vitamin D is more or less routinely prescribed nowadays for infants. But is the antiricketic routinely administered in the home? Does the child refuse it? Is it given in some unstandardized form, purchased from a false sense of economy because the physician did not specify the kind?

A uniformly potent source of vitamin D such as Oleum Percomorphum, administered regularly in proper dosage, can do more than protect against the gross visible deformities of rickets. It may prevent hidden but nonetheless serious malformations of the chest and the pelvis and will aid in promoting good dentition. Because the dosage is measured in *drops*, Oleum Percomorphum is well taken and well tolerated by infants and growing children. Rigid bioassays assure a uniform potency. Oleum Percomorphum, moreover, is a natural source of vitamins A and D.

EXIGENCY OF WAR: Oleum Percomorphum 50% is now known as Oleum Percomorphum 50% With Viosterol. The potency remains the same; namely, 60,000 vitamin A units and 8,500 vitamin D units per gram. It consists of the liver oils of percomorph fishes, viosterol and fish liver oils, a source of vitamins A and D in which not less than 50% of the vitamin content is derived from the liver oils of percomorph fishes (principally Xiphias gladius, Pneumatophorus diego, Thunnus thynnus, Stereolepis gigas, and closely allied species).

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"It is almost an aphorism that infants born of anemic mothers will become anemic by the end of the first year of life."[1]

[1] Creskoff, A. J.: The Treatment of Anemias Other Than Addisonian Pernicious Anemia, **THE PENNSYLVANIA MEDICAL JOURNAL**, Page 1698, September, 1940

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